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BIOCHEMICAL MECHANISMS IN INFLAMMATION*

BY

VALY MENKIN, M.D.

Professor of Pathology, University of Kansas City, Missouri

Inflammation is a manifestation of severe cell injury in vertebrates. Any agent that interrupts normal metabolic processes may induce an inflammatory reaction. The irritant may be of exogenous or of endogenous origin. It may be physical in nature, chemical, or viable, as in the case of a micro-organism. The sequential pattern of response is quite stereotyped. Variations are attributed either to the specific chemistry of the irritant or to the anatomical location of the lesion. Here I can give only a broad panorama of our point of view based on experimental observations gathered for thirty years. I regret that limit on space prevents me from discussing the important contributions of other investigators.

In the first place an inflammatory reaction is initiated by a disturbance in local fluid exchange (Menkin, 1940a). There is a preliminary vasoconstriction followed by a vasodilatation, and, most important of all, an increase in capillary permeability. This latter phenomenon was brought first to serious attention by Cohnheim (1889). The extent of this increased permeability is evidenced by the passage of graphite particles or of bacteria through the endothelial wall at the site of an acute inflammation (Menkin, 1931a). It is of significance to determine the mechanism of this increased capillary permeability in an inflamed area. The last word on this mechanism, as on everything else in biology, has not yet been fully settled. In 1936 it was observed that an inflammatory exudate *per se* induces an increase in capillary permeability (Menkin, 1936). There seems to exist a permeability factor in the exudate, which in turn is considered to represent the products of cell injury admixed with elements from the circulating blood. Blood serum, however, is incapable of inducing such a reaction or at least an identical pattern of response. The permeability factor present in exudates can be precipitated with 20% sodium sulphate or at half saturation with ammonium sulphate (Menkin, 1940a).

Leucotaxine

By preliminary deproteinization with pyridine or dioxan and acetone, the permeability factor was purified. Subsequently it was treated with butyl alcohol or N acetic acid (Menkin, 1938a, 1940a, 1953a) (Fig. 1). The purified product consisted of doubly refractile granules in an ill-defined matrix (Menkin, 1938a). This could at times be brought to the crystalline state as needle-like crystals, though this procedure is not always successful (Menkin, 1938a, 1940a). In addition, this substance induced first the close adherence of polymorphonuclear leucocytes to the endothelial wall, as well as their subsequent migration or diapedesis into the extracapillary spaces (Fig. 2). This migratory activity failed to occur when blood serum was extracted by the same scheme. This substance is diffusible from the whole exudate and

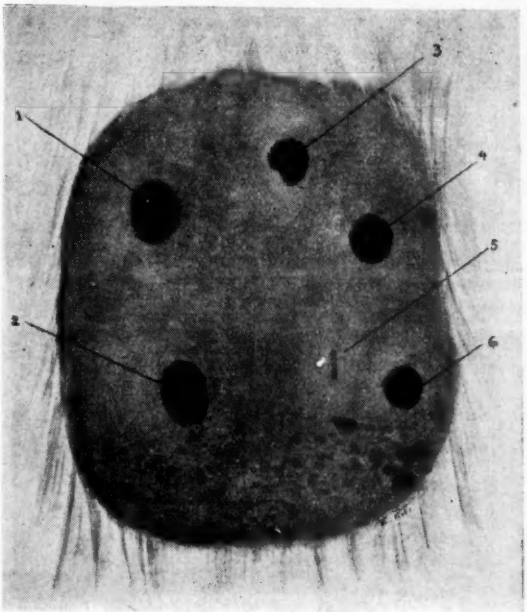

FIG. 1.—Drawing illustrating the effect of several leucotaxine fractions in increasing capillary permeability in a rabbit: *Areas 1 and 2:* Injected intracutaneously 5 mg. of fraction N in saline (for isolation cf. Menkin, 1940a, Chapter IV, p. 34). About 42 to 43 minutes after local injections of this fraction, there is marked accumulation of trypan blue from the circulating bloodstream. *Area 3:* This represents the accumulation of trypan blue owing to an increased capillary permeability 43 minutes after injection of a C–D fraction (Menkin, 1940a, p. 34). *Area 4:* Effect on permeability of capillaries produced by the local injection of a C fraction of leucotaxine (Menkin, 1940a, p. 34). The leucotaxine fraction was injected 40 minutes earlier. *Area 5:* The cutaneous injection of 0.5 ml. of saline fails to alter capillary permeability as indicated by the absence of any dye accumulating from the circulating blood 40 minutes after such an injection. *Area 6:* A C–D fraction of leucotaxine extracted from an exudate of a human being with peritonitis. Thirty-eight minutes after its cutaneous injection the dye is seen to have conspicuously localized in the treated cutaneous area.

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it is thermostable (Menkin, 1938a, 1940a). It displays two of the important biological properties of inflammation—namely, the ability of increasing capillary permeability and of inducing the migration of leucocytes (Menkin, 1938a, 1938b). It has been termed "leucotaxine" (Menkin, 1938a, 1938b).

The chemotactic property elicited by leucotaxine can be demonstrated by *in vitro* studies (Menkin, 1940a, 1955, 1956). The placing of a particle of leucotaxine on a supravitally stained smear containing polymorphonuclears from an exudate is followed by an orientation and aggregation of these cells around the particle of leucotaxine (Menkin, 1955, 1956). As controls, neither carbon particles nor iron powder are capable of inducing any such chemotactic response (Menkin, 1940a, 1955, 1956). Recently we have found that an exudate composed primarily of mononuclear phagocytes as encountered in the later or acid stage of an acute inflammation, when in contact *in vitro* with leucotaxine, likewise exhibits within a period of hours a peripheral aggregation of these phagocytes (Menkin, 1956). It is therefore conceivable that leucotaxine is perhaps also chemotactic for the mononuclear phagocytes. These cells, however, as shown by Harris (1954), are slower than the polymorphonuclears in their mobility towards an identical target. It is therefore possible that the peripheral spatial location of these cells in an inflamed area is also referable in part to leucotaxine (Menkin, 1956). Further *in vivo* observations are necessary in order to substantiate this view.

Leucotaxine appears to be a polypeptide (Menkin, 1938a, 1940a). Inactivation of its biological properties with aminopeptidase supports this view established earlier by other tests (Menkin, 1938a, 1956) (Figs. 3 and 4). Recent paper chromatographic studies by my former associate, Dr. W. Kalnins, further substantiate this view (Menkin, 1956). Whether there is a prothetic group attached to leucotaxine remains yet to be determined. A lipoidal group was considered. Lipase fails to inhibit leucotaxine. The activity appears to reside in the peptide linkages. In brief, this substance is biologically specific. It has been purified to some extent, but considerable studies are still required in order

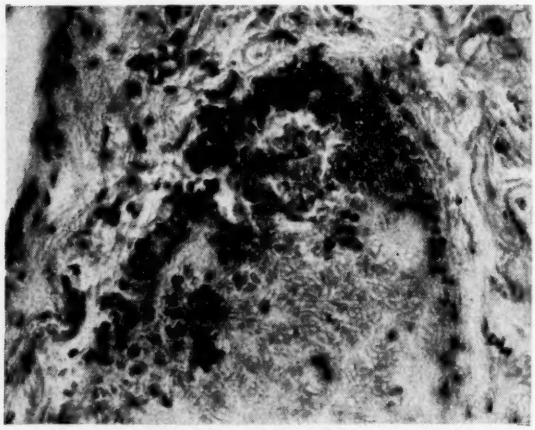

FIG. 2.—Leucotaxine, 113 μg./ml., induces not only increased capillary permeability, but likewise margination with subsequent diapedesis of polymorphonuclear leucocytes through the walls of a small venule. (×285.)

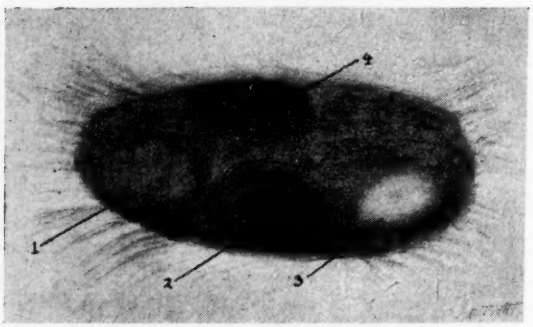

FIG. 3.—Drawing to show the effect of aminopolypeptidase in inactivating leucotaxine: *Area 1:* 2 ml. of aminopolypeptidase in 1 ml. of phosphate buffer at *p*H 8.0 incubated with 5 mg. of C-D leucotaxine fraction inactivates the ability of leucotaxine to increase capillary permeability as gauged by the failure of trypan blue to accumulate from the circulating blood into the treated cutaneous area. *Area 2:* 5 mg. of C-D leucotaxine incubated in 3 ml. of buffer at *p*H 8.0 fails to alter the capacity of leucotaxine from increasing capillary permeability as indicated by the local accumulation of trypan blue. *Area 3:* Aminopolypeptidase in 1 ml. of buffer at *p*H 8.0 induces a blanched area, and therefore, if anything, the enzyme induces only a contractility of small vessels with no evidence of any seepage of dye from the circulating blood. *Area 4:* The C-D leucotaxine fraction used above but taken up in 3 ml. of saline induces marked increase in capillary permeability as indicated by the conspicuous staining of the local cutaneous area which follows the seepage of dye from the circulating blood. The observations support the view that leucotaxine is a polypeptide which is readily inactivated by an aminopolypeptidase.

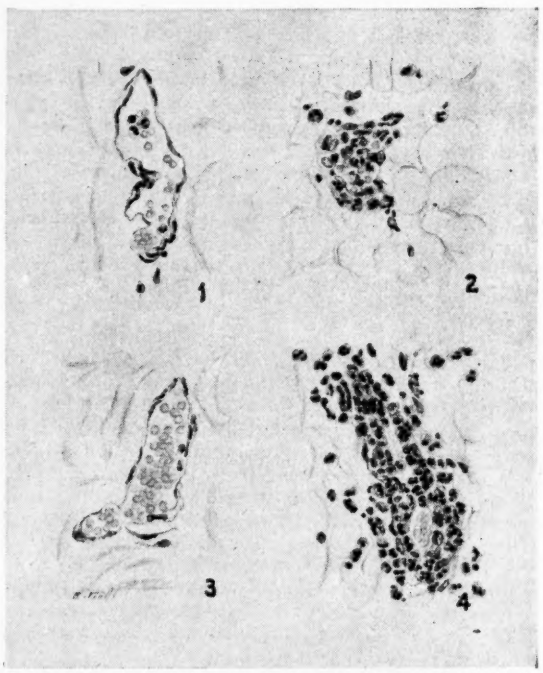

FIG. 4.—Drawing showing the inactivation of leucotaxine by both acid and enzymatic hydrolysis. *Area 1:* A capillary vessel in a cutaneous area injected with leucotaxine first hydrolysed by 50% HCl. The procedure has inactivated the ability of leucotaxine to induce leucocytic migration. *Area 2:* A capillary vessel in a cutaneous area treated with leucotaxine. Note, in contrast to the effect of acid hydrolysis in Area 1, the prominent number of polymorphonuclear leucocytes in the lumen as they are migrating outward. *Area 3:* When leucotaxine is inactivated by an enzyme such as aminopolypeptidase, there follows a conspicuous absence of any migratory activity on the part of polymorphonuclear leucocytes. *Area 4:* In contrast to Area 3, the same untreated fraction of leucotaxine induces marked chemotactic activity as indicated by conspicuous margination and diapedesis of leucocytes. The magnification utilized was about ×600.

to obtain complete purity, as well as additional chemical information concerning the precise structure of this significant biological substance. Since leucotaxine has been shown (Menkin, 1956) to be chemotactic both *in vivo* and *in vitro*, the objections recently raised again by Harris, without bringing any factual experimental data, appear to be without foundation (Harris, 1960). Similar arguments have already been presented in the past, and have been adequately treated by me (Harris, 1954, Menkin, 1955, 1956). Harris, however, in his recent review ignores these replies (Harris, 1960).

In an endeavour to throw light on the precursors in the injured cell of leucotaxine, the method of differential centrifugation was employed (Menkin, 1958a). Leucotaxine was found to be associated with the mitochondrial and often with the microsomal fraction of homogenized inflamed tissue when the exudate was at an alkaline *p*H. The mitochondrial-leucotaxine fraction displayed the same property as leucotaxine recovered from exudates—namely, repression by cortisone (Menkin, 1958a). The recovery of leucotaxine, which *per se* reproduces the properties of the untreated exudate—namely, that of increasing capillary permeability and of inducing leucocytic migration—does not preclude the possibility that other factors may also contribute to the phenomenon of increased capillary permeability at the incipient stage of the inflammatory reaction (Menkin, 1940a ; Miles and Wilhelm, 1955 ; Spector, 1956 ; Menkin, 1960).

Leucocytosis-promoting Factor

Let us now turn to another common denominator liberated by injured cells at the site of acute inflammation. Leucocytosis, or elevation in the number of circulating leucocytes, is often associated with various types of acute inflammatory conditions. The intravascular introduction of an exudate derived from the site of an inflammation of a dog with leucocytosis into a recipient dog induces in the latter a state of leucocytosis (Menkin, 1940b). Leucotaxine introduced into the circulation fails to induce such an effect (Menkin, 1940b). The rise in the number of circulating leucocytes is referable to a discharge of immature granulocytes from the bone-marrow. The evidence thus indicates that there is present a leucocytosis-promoting factor (L.P.F.) in an inflammatory exudate. Its presence reasonably explains in part the mechanism of leucocytosis with inflammation.

This specific factor is non-diffusible and it is thermolabile (Menkin, 1940b, 1940c). It can be purified by ammonium sulphate fractionation (Menkin, 1940c, 1956). It is absent in blood serum unless there is a concomitant acute inflammation (Menkin and Kadish, 1942). It causes specific hyperplasia of granulocytes and of megakaryocytes in the bone-marrow (Menkin, 1943a, 1956, 1958b). Chromatographic studies indicate that one is perhaps dealing with a polypeptide (Menkin, 1956, 1958b) ; though cataphoretic studies by Dillon, Cooper, and Menkin (1947) indicate that the L.P.F. is distributed in the α_1- and α_2-globulin.

Ageing the material causes a loss in biological potency and the L.P.F. becomes insoluble (Menkin, 1948a). Centrifugalization of the suspended aged material in an aqueous medium reveals, however, that the active principle is in the supernatant phase, and that this activity seems confined to a polypeptide structure. This substance recovered from canine exudate is likewise active in human beings (Menkin, 1946a, 1956). This may prove to be of clinical significance in various states of persistent leucopenia that are accompanied with only some degree of aplasia of the haematopoietic tissue in the marrow (Menkin, 1946a). Recent studies by differential centrifugation indicate that the L.P.F. is found in association with the most soluble phase or S_2 fraction of inflamed tissue when the latter is homogenized in 0.25 M sucrose (Menkin, 1958a). The L.P.F. can also be obtained as a result of cellular injury as obtained by homogenizing various tissues—for example, liver, spleen, kidney, or muscle. From the saline extract of these homogenates the L.P.F. can be recovered (Menkin, 1956).

Immunological Implications of Inflammation

I should like now to divert, in brief, attention to the immunological implications of inflammation. This, in the last analysis, is the most important aspect of this basic defence reaction. If any viable or non-viable

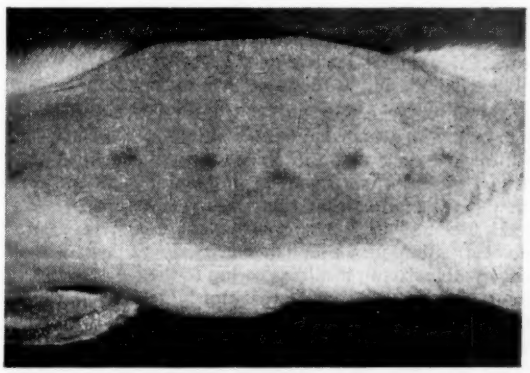

FIG. 5.—Effect of leucotaxine extracted from exudates in the incipient stage of an inflammation. Four skin areas are shown on the abdomen of a rabbit in which after the local injection of leucotaxine into each area there followed an increased capillary permeability as indicated by prompt accumulation of trypan blue from the blood into each cutaneous area. Leucotaxine was extracted from the first available exudates 4½ to 5 hours after the injection of an irritant into the pleural cavity of a dog. This observation indicates that as soon as an exudate can be recovered, even amounting only to several millilitres, leucotaxine can already be shown to be present in such material.

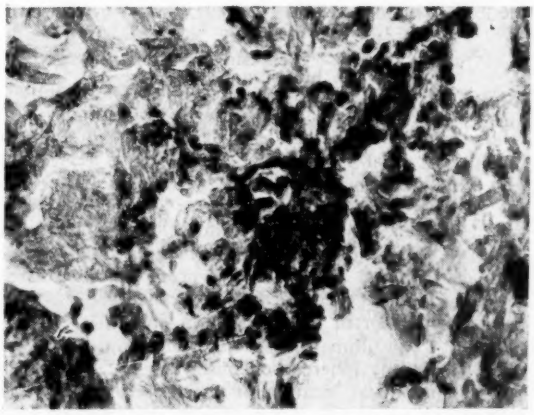

FIG. 6.—From the earliest available exudate after the injection of an irritant, leucotaxine can be extracted. In such a 4½-hour-long inflammation extracted leucotaxine not only induces increased capillary seepage (cf. Fig. 5), but it also causes conspicuous local migration of polymorphonuclear leucocytes. (×285.)

agent is injected into an acutely inflamed area the foreign material is held fixed in the area of injury, so that it is now incapable of draining into the tributary lymphatics (Menkin, 1940a). On the other hand, when such material is injected intravenously it penetrates readily into the site of an acute inflammation (Menkin, 1940a). This is primarily due to the local increase in capillary permeability which, in the incipient stage, is largely referable to the liberation of leucotaxine by the injured cells. Leucotaxine can be identified during the first four to five hours of inflammation, when an exudate is still very scant in amount (Figs. 5 and 6). If various unrelated types of material such as a dye, a protein, graphite particles, or ferric chloride are injected into the normal peritoneal cavity they readily drain into the retrosternal lymphatic vessels. However, the induction of a peritonitis by an irritant fails after a critical interval or threshold to cause the subsequent absorption of injected substances from the inflamed peritoneal cavity as rapidly as under normal circumstances (Menkin, 1940a, 1956). This retention or fixation at the site of inflammation is referable to the deposition of a fibrinous network and to the presence of local thrombosed lymphatics (Menkin, 1931b, 1940a). There is no time to discuss all the implications of this concept.

Many years ago, by studying the relative speed and intensity with which lymphatic blockade is induced by various pyogenic micro-organisms, it was concluded that acute inflammation from an immunological point of view is the regulator of bacterial invasiveness (Menkin, 1933, 1935, 1940a). The observations presented a paradoxical situation. Staphylococci are, at least to an appreciable extent, localized owing to their marked local injurious effect that causes prompt lymphatic blockade. On the other hand, haemolytic streptococci appear to owe their penetrating or invasive properties to their relatively mild local injurious effect. This tends to maintain the patency of the lymphatics for a period of 48 hours or thereabouts. During this interval the streptococci are unobstructed in their dissemination. A concept, as a result of these observations, can be formulated as follows: $D=\frac{kt}{I}$; where D refers to dissemination, t to time, and I to the degree of induced local injury. k is a constant which may be determined by the type of irritant or by the anatomical location of the lesion (Menkin, 1940a, 1956).

Necrosin

As stated at the beginning of the presentation, inflammation is considered to be a manifestation of cellular injury in vertebrates. The basic pattern was first described at the beginning of our era by Celsus. This entails the well-known classical signs of rubor, tumor, calor, and dolor. Galen and later John Hunter added another cardinal sign—namely, loss in function. We have pointed out the presence of an additional biochemical cardinal sign—namely, proteolysis (Menkin, 1942a). It there a chemical factor concerned with the basic mechanism of the pattern of injury in inflammation? The ultimate character of the injury may be modified by the inherent chemistry of the irritant or by the anatomical location of the lesion. In brief, a number of years ago it was found that the primary reaction seems to be referable to a toxic euglobulin liberated by injured cells at the site of inflammation, and which I have termed "necrosin" (Menkin, 1943). The α-globulins of exudates containing the L.P.F. are inactive in inducing any such characteristic lesion. The euglobulin of blood serum is likewise inactive (Menkin, 1943b, 1956).

The first morphological type of injury induced by necrosin affects the collagenous bundles. Within 10 minutes these may be swollen (Menkin, 1943b). Necrosin induces the formation of thrombi in lymphatics. The significance of lymphatic blockade in inflammation, as described above, may therefore well be referable to the liberation of necrosin by the severely injured cells. Thrombi in small blood vessels may likewise be found at the site of the acute injury (Menkin, 1943b, 1946a, 1956). Intravascular injections of necrosin frequently induce hepatic injury (Menkin, 1943b, 1946a, 1956). Repeated injections into dogs of necrosin in an endeavour to duplicate a prolonged acute process may be followed by a curious denudation of the cytoplasmic contents of liver cells (Fig. 7) (Menkin, 1946a). There is a replacement by glycogen as evidenced by appropriate cytochemical staining (Best carmine). This glycogen deposition does not seem to be referable to diet (Menkin, 1946a). Starving an animal for one or even sometimes two days yields the same abundance of glycogen in the liver of a dog repeatedly injected with necrosin. The kidney is another organ that may be frequently involved after repeated injections of this substance (Menkin, 1943b, 1946a). This may be in the form of damage to the lining epithelium of the tubules and to the irregular presence of foci of leucocytic infiltration. Recently we have found that repeated intravenous injections of necrosin or of a diffusible component from exudate often induce amyloid formation in the spleen, liver, and kidneys. This is being studied further in an endeavour to find out whether amyloid is referable to a by-product liberated by injured cells at the site of inflammation (Menkin, 1958c).

The euglobulin fraction of inflammatory exudates at an acid *p*H contains three additional chemical factors which have definite biological significance in inflammation. It was noted in the early days of our studies on this fraction of exudate that, in addition to inducing injury, leucopenia, leucocytosis, and fever were frequent accompaniments after the injections into dogs of this

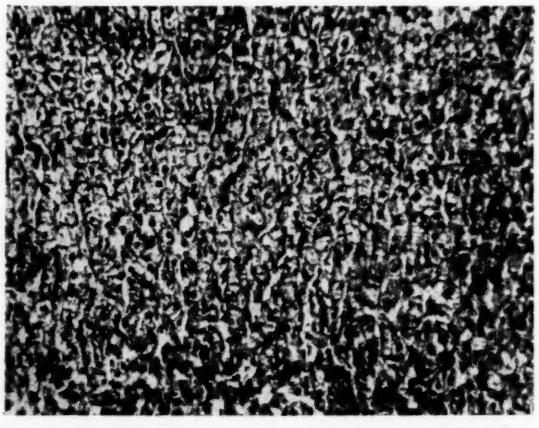

FIG. 7.—Liver of a dog that had received six intravascular injections of necrosin. Many of the hepatic cells seem denuded of their cytoplasmic contents. This appearance is referable to an abundance of glycogen deposits which are not nutritional in character. (×157.)

toxic euglobulin (Menkin, 1943b). This, as mentioned, is particularly true when the euglobulin is derived from acid exudates (Menkin, 1956).

Pyrexin

Let us examine, in brief, the primary mechanism of fever with acute inflammation. First, it is noted that the whole euglobulin fraction of exudates fails to enter readily into solution in the presence of electrolytes. This is contrary to the usual behaviour of euglobulins. Further studies have indicated that after precipitating out the euglobulin at one-third saturation with ammonium sulphate prior to dialysing out the sulphate ions, the precipitate may be treated with distilled water. Under such circumstances, a true euglobulin is found to enter into solution in the presence of the sulphate ions (Menkin, 1945). This euglobulin is necrosin. The residual insoluble fraction contains the pyrogenic factor. By this simple dissociation we have succeeded in separating necrosin from the fever-inducing factor, that has in turn been termed "pyrexin" (Menkin, 1945). At times this dissociation is not readily performed. One can then resort to merely allowing necrosin in the fluid state to stand in the refrigerator; this causes, within a few days to a few weeks, the sedimentation of pyrexin to the bottom of the container (Menkin, 1956).

Pyrexin has also been crystallized from a 50% acetic mother liquor (Menkin, 1952). The crystals appear to be rhomboid, but on slight dehydration they tend to assume a needle-like appearance. These crystals are active in inducing fever in rabbits, in contrast to the ineffectiveness of the mother liquor (Fig. 8). Necrosin contains proteolytic activity, especially when fibrinogen is utilized as a substrate (Menkin, 1946b). It is interesting to note that the incubation of necrosin is often followed by an end-product which is *per se* pyrogenic (Menkin, 1945, 1956). Conceivably, pyrexin in the euglobulin fraction of exudates may perhaps be an end-product of proteolytic activity of necrosin. Recent differential centrifugation studies indicate the presence of two pyrogenic factors at the site of inflammation and concerned in the pathogenesis of fever: one is pyrexin (thermostable) and another is thermolabile (Menkin, 1958a). It is suggested that the latter is similar to, if not identical with, the factor actively being studied by Beeson, Wood, and Bennett (Bennett and Beeson, 1953; King and Wood, 1958).

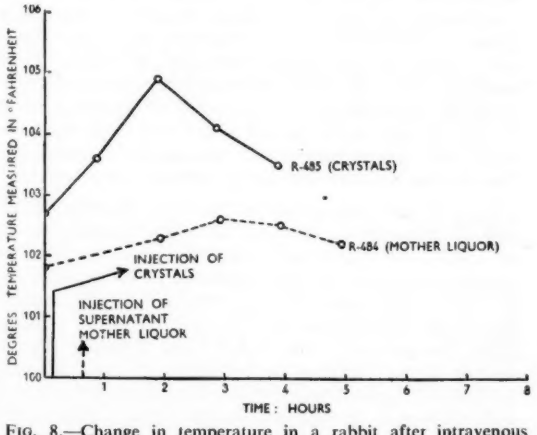

FIG. 8.—Change in temperature in a rabbit after intravenous injection of a suspension of pyrexin crystals. ——, The course of the fever after injection of the crystalline suspension; – – –, the supernatant 50% acetic acid mother liquor fails to induce an effect similar to that obtained with the crystals. (From Menkin, 1952.)

I have given a general picture of the inflammatory reaction by illustrating how the liberation by injured cells of various chemical factors or mediators reasonably explains the biological manifestation of this important process. It can be viewed as the physical basis of infectious disease, even though inflammation in itself is a much more inclusive term, and, as pointed out above, may be caused by non-viable irritants as well. There are other factors, such as the thermostable leucocytosis factor (Menkin, 1949, 1950a) and the two leucopenic factors (Menkin, 1946c, 1948b). Some of these mediators are also recovered in the euglobulin fraction of acid exudates (Menkin, 1956). There is no time, however, to enter into a description of the other already identified factors. These have been adequately described elsewhere (Menkin, 1950b, 1956). We are beginning to shed light on the cytological precursors of these significant chemical mediators (Menkin, 1958a). It may well be that Ungar's (1953) view that histamine liberation is referable to the activity of a protease may perhaps also prove to apply to the formation of the various chemical mediators of inflammation identified by me (Menkin, 1956). These factors are biologically very specific. For instance, pyrexin induces fever, whereas the injection of the L.P.F. is followed by leucocytosis. These factors, however, are not as yet chemically pure, for even crystallization is not a criterion of purity (Shedlovsky, 1943). Their further purification looms as an important task for the future (Menkin, 1956).

As a central idea I should like to restate to you a biochemical view of inflammation—namely, that the liberation of chemical mediators by injured cells at the site of inflammation reasonably explains the diverse biological manifestations of this basic immunological process. Finally, inflammation can be regarded as an admirable system to study the biochemistry of injured cells.

The Anti-inflammatory Problem

Before terminating this discussion I wish to describe, in brief, an additional feature in the biology of inflammation. In other words, it would be well to say something about the anti-inflammatory problem. In 1940 I made the first report on the repressive effect of the adrenal cortical extract to the increased capillary permeability induced by an exudate or its contained leucotaxine (Menkin, 1940d). The same suppression was shown to occur with compound E, which eventually came to be known as cortisone (Menkine, 1942b). These were the first experimental observations on the anti-inflammatory property of cortisone.

In 1950, subsequent to the brilliant discovery by Hench, Kendall, Slocumb, and Polley (1949), at the Mayo Clinic, on the usefulness of cortisone and A.C.T.H. in arthritis, our earlier studies on this problem were resumed. We then found that neither adrenal nor cortisone repressed the increase in capillary permeability induced by an acid exudate (Menkin, 1951a). This, however, was readily suppressed by A.C.T.H. (Menkin, 1951b). There are thus at least two factors concerned in the mechanism of increased capillary permeability in inflammation: (*a*) leucotaxine, predominantly present in the initial or alkaline stage of development of the inflammatory reaction, and the activity of which is

suppressed by cortisone; and (*b*) another factor termed "exudin," present in the later or acid stage (but independent of the *p*H) (Menkin, 1951a, 1951c). Exudin is found to be readily inhibited by A.C.T.H. but not by cortisone (Menkin, 1951a, 1951b). Crude exudin is thermolabile, non-diffusible, and has a nitrogen content of about 10%. Recent studies by differential centrifugation indicate that exudin can be isolated as a nucleopeptide, and as such is repressed by both aminotripeptidase and ribonuclease (Fig. 9) (Menkin, 1959a, 1959b). Its liberation and recovery in acid exudates reasonably explains the continuous seepage of fluid in the extracapillary spaces throughout the duration of an acute inflammation. In contrast to leucotaxine, exudin fails to induce within an hour any appreciable migration of leucocytes.

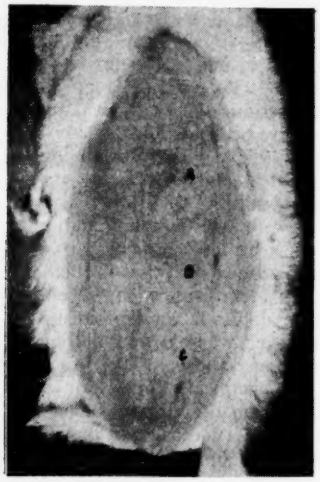

FIG. 9.—Enzymatic inactivation of purified exudin as a nucleopeptide. *Area A:* The effect of exudin, as a purified nucleopeptide, on capillary permeability—note the accumulation of trypan blue from the circulating blood into the treated cutaneous area. *Area B:* The same nucleopeptide as in Area A, but after incubation for one hour with aminotripeptidase. The effect on capillary permeability has to a large extent been eliminated. *Area C:* This nucleopeptide incubated for one hour with ribonuclease is followed by its complete inactivation. There is no dye accumulation from the circulating blood. After the injections of the material into areas A, B, and C, 5 ml. of 1% trypan blue in saline has been injected intravenously. These observations substantiate the view that exudin in the present state of purification is a nucleopeptide.

Perhaps a few words should be said about the shift in local reaction in an inflamed area. As the inflammatory reaction progresses, the exudate shifts from an alkalinity to an acidity—that is, from a *p*H of 7.2 or thereabouts to a *p*H of 6.8 or even lower. The local acidosis is referable to a glycolytic process at the site of the inflammation resulting in a lactic acid acidosis (Menkin and Warner, 1937). The polymorphonuclears are incapable of surviving this rise in hydrogen-ion concentration, and they are replaced by macrophages (Menkin, 1934, 1956). If the *p*H falls to still lower levels, all types of cells are affected, and suppuration ensues. Pus formation is virtually a function of the hydrogen-ion concentration in an acute inflammation. As stated elsewhere, these observations correlating *p*H and the cytological picture in inflammation have been confirmed in several laboratories, despite Harris's recent unwarranted assertion to the contrary (Menkin, 1956; Harris, 1960).

Exudin had been purified by repeated precipitation with ammonium sulphate at one-third saturation (Menkin, 1951a). It can at times be obtained in the crystalline state by maintaining it in the refrigerator after the addition of N acetic acid to the pseudoglobulin-albumin fraction of an acid exudate (Menkin, 1956). It has been obtained after dialysis of an exudate followed by treatment of the residual fraction with 95% alcohol. The resulting precipitate is discarded and the supernatant is found to contain exudin. But, as just mentioned, it has been most recently identified as a nucleopeptide (Menkin, 1959a, 1959b).

The suppressing action of A.C.T.H. on exudin seems to be a direct effect (Menkin, 1957a, 1957b). This does not controvert the classical view that A.C.T.H. acts via the adrenal cortex. In inflammation, however, there is such an extensive increase in local capillary permeability that some, and only some, A.C.T.H. injected into the blood-stream enters the site of an acute inflammation, and, once there, it can act directly on exudin (Menkin, 1956, 1957a, 1957b). In further support of this view, adrenalectomized rats display the same type of activity when injected with exudin and A.C.T.H. (Menkin, 1956, 1957a, 1957b). The question of any impurity in the commercial A.C.T.H. preparation utilized, such as vasopressin, has been eliminated by the use of Li's α-corticotrophin (Menkin, 1957a, 1957b). With his presumably pure fraction of A.C.T.H. we have obtained essentially the same inhibitory effect as with commercial A.C.T.H.

Cortisone penetrates from the systemic circulation into the site of an acute inflammation (Menkin, 1953b). This can be demonstrated by testing the exudate of a rabbit previously injected several times intravenously with cortisone, and comparing in another rabbit its reducing effect on the local passage of trypan blue with that of a control exudate. With the accumulation of the corticoids in an inflamed area there is likewise a suppression of diapedesis (Menkin, 1953b). It can also be demonstrated that repeated injections of A.C.T.H. into the circulating blood reduces the potency of exudin present in the exudate at the site of inflammation (Menkin, 1953c).

With the above information on hand, a study was undertaken in an endeavour to determine the anti-inflammatory mechanism. First, it was shown that cortisone tends to suppress cell activity in an invertebrate form (Menkin, 1953d). This was done by observing the reduction in the incidence of cell division after exposure of sea-urchin ova to corticoids prior to their fertilization. The data and interpretation on an invertebrate system cannot be readily transferred to as complicated a process as inflammation in vertebrate animals. Nevertheless, the observations on sea-urchin eggs (*Arbacia punctulata*) provided an idea. Is it possible that the anti-inflammatory mechanism is primarily referable to a suppression of cellular activity of injured cells at the site of inflammation so that now these cells are incapable of adequately forming the chemical factors that essentially constitute inflammation?

Experiments were set up to determine whether detectable or measurable amounts of active leucotaxine or of L.P.F. can be formed by the injured cells after repeated injections of hydrocortisone direct into the site of an acute inflammation (Menkin, 1954, 1956). Recovered leucotaxine was diminished in its activity (Figs. 10 and 11). The L.P.F. was likewise demonstrated to be reduced in its potency. The *in vitro* mixture of hydrocortisone (compound F) and the L.P.F. fails to reduce the activity of the L.P.F. This would indicate that the corticoid does not interact with the L.P.F., but rather that the formation of this factor by the injured cell is actually impaired (Menkin, 1954, 1956). *In conclusion,* the anti-inflammatory mechanism can be considered at a cellular level. By suppressing

the injured cell in its formation of the chemical factors or mediators involved in inflammation the inflammatory process is definitely reduced. From my point of view, it is the factors that are liberated by the injured cells which constitute inflammation. The corticoids appear to suppress the activity of the injured cells in forming these very chemical mediators.

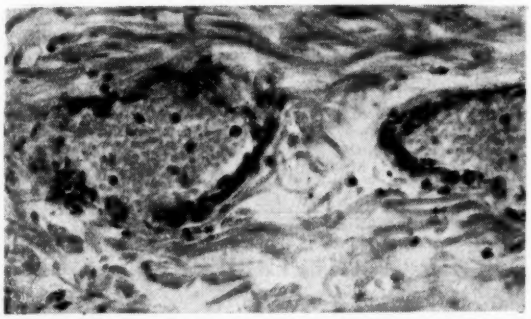

FIG. 10.—Effect of leucotaxine in inducing the margination of polymorphonuclear leucocytes about one hour subsequent to the injection of the substance in turn extracted from a sample of canine exudate. (×253.) (From Menkin, 1956.)

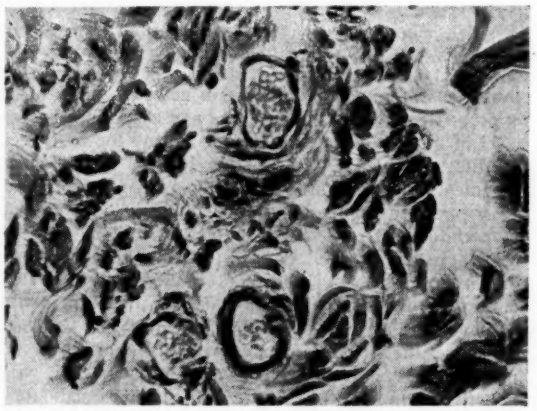

FIG. 11.—Effect on the potency of leucotaxine of two successive daily injections of hydrocortisone (compound F) into an inflamed area, amounting to a total of 40 mg. of commercial hydrocortisone. Leucotaxine was extracted from the exudate of such a treated inflamed area in the pleural cavity of a dog. Note the inability of the leucotaxine to induce leucocytic migration (cf. Fig. 10). This leucotaxine fraction, following the two hydrocortisone injections, likewise failed to increase capillary permeability. (×289.) (From Menkin, 1954.)

TABLE I.—*Sequences in the Development of the Inflammatory Reaction*

1. *Disturbance in local fluid exchange:*
   - (*a*) Initial increased capillary permeability. Referable to liberation of leucotaxine, a crystalline nitrogenous substance; suppressed by cortisone.
   - (*b*) Initial increase in lymph flow.
   - (*c*) Subsequent increased capillary permeability. Referable to exudin, in turn suppressed by A.C.T.H.
2. *Localization of irritant (fixation),* referable to lymphatic blockade by occluding thrombi and a fibrinous network at the site of severe inflammation:
   The inflammatory reaction may be regarded as the regulator of bacterial invasiveness—that is, $D=\frac{kt}{I}$, where D refers to dissemination; I, to degree of local injury; t, to time; and k is a constant.
3. *Migration of leucocytes:*
   - (*a*) Diapedesis of polymorphonuclear leucocytes, referable to liberation of leucotaxine.
   - (*b*) Cytological sequence at the site of inflammation conditioned by the local *p*H, in turn referable to a disturbance in carbohydrate metabolism; glucose formed by injured cells by deamination of proteins.
   - (*c*) Leucocytosis in the circulation, referable to two factors:
     1. Liberation of a thermolabile leucocytosis-promoting factor (L.P.F.) demonstrable in association with the pseudoglobulin fraction of exudates. The L.P.F. induces a concomitant growth of granulocytes and megakarocytes in the bone-marrow.
     2. A thermostable L.P.F. associated with the euglobulin fraction of acid exudates.
4. *The pattern of injury in inflammation,* referable to the liberation of a toxic substance in the euglobulin fraction of exudates, termed necrosin. This fraction contains proteolytic activity.
   - (*a*) Fever with inflammation, referable to liberation of pyrexin, a thermostable factor, in exudative material. Apparently a thermolabile pyrogenic factor is also present.
   - (*b*) Leucopenia with inflammation associated with the liberation of a leucopenic factor in acid exudates and with leucopenin, liberated in alkaline exudates. Pyrexin, the leucopenic factor, and the thermostable leucocytosis factor are, with necrosin components, recovered from the euglobulin fraction of usually acid exudates.
5. *Repair,* referable to the liberation of a growth-promoting factor in exudates. The factor is a diffusible component in exudative material, and appears to be consistent with being a nucleopeptide.

To conclude this lengthy discussion, an integrated summary of the principal sequences concerned in the development of an inflammation is shown in the accompanying Table I. The various mediators liberated by the injured cell are shown in Fig. 12. I hope that

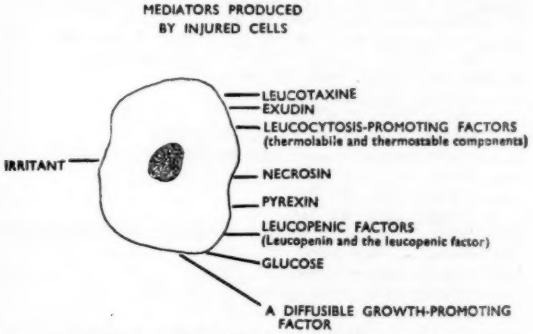

FIG. 12.—Revised and modified from a drawing in *Science*, 1947, **105**, 538, and from Menkin (1956).

interest in probing further into the biochemistry of the injured cell may have been aroused by this panoramic discussion of inflammation, a phenomenon that has always been considered of basic importance in the study of pathology.

Summary

Inflammation is a manifestation of severe cell injury in vertebrates. The inflammatory reaction is initiated by disturbance in local fluid exchange. The most important alteration is a local increase in capillary permeability. This is brought about in large part by the liberation of leucotaxine by injured cells at the site of inflammation. This is a diffusible substance which appears to be a polypeptide. It has also the property of inducing the migration of leucocytes through the endothelial wall. Another mediator present in inflammatory exudates is termed the leucocytosis-promoting factor (L.P.F.). This factor, in addition to the

thermostable leucocytosis factor, provides a reasonable explanation for the mechanism of leucocytosis in inflammation.

The immunological implication of inflammation is discussed, and it is pointed out that the role of inflammation is that of a regulator of bacterial invasiveness. The pattern of injury in inflammation is ascribed to the liberation of a toxic euglobulin termed necrosin. Fever is shown to be due to two factors—namely, a thermostable component termed pyrexin, and a thermolabile factor.

The studies on the anti-inflammatory problem, first described by me in 1940 and 1942, are summarized ; and it is shown that the mechanism of action is referable to a suppression of cellular activity. The injured cell is incapable of forming the mediators of inflammation as readily as under normal circumstances.

A summary of the development of the inflammatory reaction as well as concluding remarks on the significance of the biochemistry of inflammation are pointed out.

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NEONATAL HYPERBILIRUBINAEMIA*

BY

ALBERT E. CLAIREAUX, M.D., F.R.C.P.Ed.

Consultant Morbid Anatomist, Bernhard Baron Memorial Research Laboratories, Queen Charlotte's Maternity Hospital, London

[WITH SPECIAL PLATE]

Jaundice is commonly observed in newborn infants. It is probable that 40% of infants have a serum bilirubin level of at least 4 mg. per 100 ml. during the first week of life. For this reason the term "physiological jaundice" has crept into use. This is an unfortunate description, as it tends to minimize the risk to the patient. Hyperbilirubinaemia can be dangerous or even lethal in certain patients. The danger lies in the development of cerebral nuclear jaundice (kernicterus). This may either kill the infant or leave him with permanently damaged areas in the brain. It must be stressed, therefore, that in certain circumstances jaundice in the newborn period is to be regarded as pathological and of serious import for the future of the child. Fortunately, hyperbilirubinaemia of this magnitude is not common in the absence of an actual disease process such as haemolytic disease of the newborn. The danger is that the necessary corrective treatment will be instituted too late if jaundice in otherwise normal infants is regarded as being entirely physiological.

The nature of the bile pigment responsible for the hyperbilirubinaemia is of diagnostic and prognostic significance. Ehrlich's method for demonstrating the presence of bilirubin in urine was adapted by van den Bergh and Snapper (1913) for the estimation of bilirubin in plasma It was later found (van den Bergh and Muller, 1916) that alcohol was not an essential for the development of the colour reaction when bile was used or if the patient was suffering from obstructive jaundice. In patients suffering from haemolytic jaundice alcohol was still necessary, and the reaction was called "indirect." The direct and indirect forms of the van den Bergh reaction have been used for many years in the diagnosis of obstructive and non-obstructive jaundice. It was not clear, however, whether two separate bile

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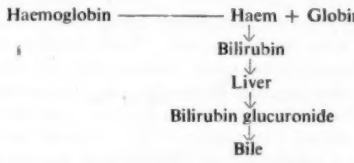
pigments were involved, or whether bilirubin was in some way bound to protein in haemolytic jaundice and had to be freed by alcohol before a reaction could occur. Some years earlier Schmörl (1904) had examined a number of cases of kernicterus and was struck by the fact that the yellow areas in the brain did not turn green when preserved in formalin, whereas liver tissue in cases of cirrhosis did so. He was among the first to suggest that there were probably two types of bile pigment in the body. It was also observed that neurological complications did not occur in congenital obstruction of the bile-ducts. Cole and Lathe (1953) were able to identify two separate bile pigments in plasma from jaundiced patients. One pigment gave a direct reaction with the van den Bergh test, and was water-soluble. It was present in the plasma of patients with obstructive jaundice, and was the main pigment in human bile. The other pigment was obtained from patients with haemolytic jaundice. This pigment gave an indirect reaction with the van den Bergh test, was insoluble in water, and proved to be bilirubin itself. The direct-reacting pigment was then found to be a glucuronide of bilirubin (Billing *et al.*, 1957). The nature of this pigment was confirmed by Schmid (1956) and Talafant (1957).

Meanwhile Claireaux, Cole, and Lathe (1953) were able to show that the pigment responsible for the yellow staining of areas in the brain in kernicterus was also bilirubin. Samples of brain from the pigmented areas were extracted in solvent systems, and the pigment was separated by reverse-phase partition chromatography. The extracted pigment was identified spectrophotometrically.

The probable metabolic pathways leading to the conjugation of bilirubin with glucuronic acid have been outlined by Billing and Lathe (1958) and Schmid (1958). Uridine diphosphate glucuronic acid and bilirubin are acted upon by an enzyme, bilirubin glycuronyl transferase, with the production of bilirubin glucuronide and uridine diphosphate. The enzyme system responsible for the conjugation of bilirubin is present in the microsomes of the liver cell (Lathe and Walker, 1957). Activity of this enzyme is low in the liver of the newborn baby (Vest, 1958), in congenital non-haemolytic jaundice (Peterson and Schmid, 1957), and in the Gunn strain of jaundiced rats (Axelrod *et al.*, 1957) and the newborn animal (Brown *et al.*, 1958). Conjugation would appear to be essential for the excretion of bilirubin, though Schmid (1958) points out that a small fraction of bilirubin glucuronide in human bile is possibly hydrolysed to bilirubin either as a result of enzyme activity or on account of the alkalinity of the medium. Recently Isselbacher and McCarthy (1959) have suggested an alternative pathway for the excretion of bilirubin. Bilirubin sulphate has been identified in the bile of rats, cats, and man. The sulphate appears to be linked at the hydroxyl group, in contrast to carboxyl-group linkage of the glucuronide. The sulphate-conjugated fraction contains no glucuronic acid and is alkali-stable. A further unidentified fraction of bile pigment which does not contain glucuronic acid and is alkali-labile would also appear to exist. It is unlikely, however, that these fractions together make up a large part of the total bile pigment, and the majority of the latter is excreted as a glucuronide.

The capacity of the newborn infant's liver to form glucuronides has been studied by Vest (1958). Acetanilide was administered to full-term and premature babies and the acetyl *p*-aminophenol glucuronide conjugate estimated in the urine. He found that adults and older children are able to excrete 80% of the test substance in 24 hours. Newborn infants, especially if premature, excrete only a small amount in 24 hours, and less than 10% in 48 hours. Normal function is gradually achieved during the first three months of life. It was also observed that there was an inverse relationship between the ability to form glucuronide and the height of the serum bilirubin. The rate at which conjugation occurs in the body has also been studied in infants by the estimation of acetyl *p*-aminophenol glucuronide in the blood. After a dose of acetanilide the blood concentration of the conjugate reaches a peak in four hours in the adult and in 11 hours or more in the newborn infant (Vest and Streiff, 1959). Since the enzyme system of the infant's liver responsible for the conjugation of *p*-aminophenol with glucuronic acid is also thought to be responsible for conjugating bilirubin, it is assumed that the latter is similarly delayed in the newborn infant. The author thus concludes that jaundice in the newborn, in the absence of an actual disease process, is the result of an insufficiency of glucuronic acid transferase activity in the liver.

Bilirubin in the first place is derived from haemoglobin. The latter is broken down by the cells of the reticulo-endothelial system, and the original tetra-pyrrol ring is split up to form a chain of four pyrrol rings known as bilirubin. This can be described diagrammatically as follows:



Bilirubin is then transferred to the liver cells, where two molecules of glucuronic acid are attached. This achieves two things: (1) it renders bilirubin water-soluble, and so it can be readily excreted; and (2) it renders it non-toxic.

There is thus abundant justification for the old division of cases of neonatal jaundice into non-

Conditions Leading to Jaundice in the Newborn

Condition	Type of Blood Pigment	Neurological Complications
Non-obstructive jaundice:		
Functional immaturity of liver	Bilirubin	Kernicterus probable
Haemolytic disease (erythroblastosis)	,,	,, frequent
Congenital spherocytosis (acholuric jaundice)	,,	,, rare
Congenital familial non-haemolytic jaundice	,,	,, possible
Congenital myxoedema (cretinism)	,,	,, ,,
Obstructive jaundice:		
Congenital bile-duct atresia	Bilirubin glucuronide	None
Haemolytic disease (persistent jaundice)	,, ,,	,,
Tumour	,, ,,	,,
Cystic fibrosis of pancreas	,, ,,	,,
Galactosaemia	,, ,,	No kernicterus, but mental defect
Infection (bacteria, viruses, protozoa)	Bilirubin and bilirubin glucuronide	Kernicterus rare

obstructive and obstructive types. It must be said, however, that prematurity itself tends to complicate the picture. If an infant has an organic type of disease leading to an obstructive form of jaundice and that infant is also premature, both forms of bilirubin will be found in the blood. The various conditions leading to jaundice in the newborn are shown in the Table.

A. NON-OBSTRUCTIVE JAUNDICE

So far as Great Britain and probably North America are concerned the two common forms of non-obstructive jaundice in the newborn are associated either with functional immaturity of the liver or with haemolytic disease.

1. Functional Immaturity of the Liver

This is the condition formerly known as physiological jaundice, and as a rule the more immature the infant the higher the serum bilirubin and the later the time at which normal liver conjugation of bilirubin to its glucuronide begins. Cunningham (1959) studied the bilirubin in 1,000 babies. Of these, 63 were premature, and in 11 the bilirubin level reached 15 mg. per 100 ml. or over. Among babies weighing more than 2,500 g. at birth the bilirubin level was over 10 mg. per 100 ml. in only 2%. Haemolytic disease had been excluded among the cases in the series. Bowman *et al.* (1957) reported a similar series with a rather higher incidence of bilirubin levels in the upper range: 14% were over 20 mg. and 7% over 25 mg. per 100 ml. As the lesion is thought to be a pure enzyme deficiency, no structural change is seen in the liver in fatal cases. Apart from a few foci of normoblasts, histological examination of the organ reveals nothing (Special Plate, Fig. 1). In a few infants the serum bilirubin rises to a high level and kernicterus develops. About one-quarter of the cases of kernicterus reported by Claireaux *et al.* (1953) were associated with functional immaturity of the liver only.

2. Haemolytic Disease of the Newborn

This results from blood incompatibility between mother and foetus. Usually the rhesus blood group is involved, but other systems such as A-B-O, Kell, Duffy, Lewis, etc., may occasionally be incriminated. In this condition serum bilirubin levels may become extremely high—up to 40 mg. per 100 ml. or more—and in the untreated case kernicterus is apt to develop. In fatal cases the liver is enormously enlarged and the cut surface is reddish-brown in colour. The spleen is also usually much enlarged. On histological examination the hepatic cells are almost obscured by enormous numbers of haemopoietic foci composed of normoblasts and erythroblasts (Special Plate, Fig. 2). Large leucopoietic collections of cells are seen in the portal tracts. The liver cells and Kupffer cells contain haemosiderin, and the Prussian-blue reaction is positive (Claireaux, 1950).

3. Congenital Spherocytosis (Acholuric Jaundice)

This disorder is seldom very severe in the newborn period. It is associated with a congenital defect in the red blood corpuscles which renders them unduly fragile. Haemolysis begins in 0.6% saline and is complete at 0.45%. The spleen is enlarged, and the bone-marrow shows very active erythropoiesis. As a rule the anaemia is moderate, and jaundice seldom reaches dangerous proportions. Occasionally, however, very high serum bilirubin levels are observed. In the cases reported by Adams (1954) the bilirubin rose to 21 mg. per 100 ml., and a previous sibling had died with kernicterus. Stamey and Diamond (1957) have reported four cases of congenital spherocytosis where severe jaundice was encountered during the first 36 hours of life.

4. Congenital Familial Non-haemolytic Jaundice

This is a rare condition first described by Crigler and Najjar (1952). Seven infants of three consanguineous families were noted to have been severely jaundiced in the neonatal period. These infants were not premature, did not have haemolytic disease, and had no infection. They were jaundiced from birth and had a serum bilirubin level of 23–45 mg. per 100 ml. The majority died within one year, and had neurological abnormalities. One was shown to have kernicterus. Two survivors were reported by Childs and Najjar (1956). These have a permanent serum bilirubin level of 25 mg. per 100 ml. They are of normal height and weight for their age, and the liver and spleen are of normal size. Among the fatal cases necropsy revealed little abnormal. Some bile thrombi were present in the liver, and in one case a mild portal fibrosis was noted. Schmid *et al.* (1957) have investigated the bile in three children with this disorder. According to their report a general defect in glucuronide production would seem to be the basic abnormality. A similar group of patients has been studied by Childs *et al.* (1959). All patients showed a marked impairment in glucuronide conjugation. A conjugation defect midway between that of the patients and normal controls was observed in the majority of the relatives. The authors believe that the gene responsible for the disease is recessive in respect to the jaundice, but shows incomplete dominance so far as glucuronide conjugation is concerned.

5. Congenital Myxoedema (Cretinism)

Prolonged jaundice in three cases of congenital myxoedema was reported by Åkerrén (1954). The patients' general condition improved after treatment with thyroid extract and the jaundice vanished. Kernicterus has not been reported with certainty in this condition, but Christensen (1956) has described a case in which the serum bilirubin reached 21 mg. per 100 ml., and defective vision, hearing, and intellect were suspected. It has been suggested that lack of thyroid hormone has an inhibitory effect on the enzyme systems responsible for the conjugation of bilirubin (Lathe *et al.*, 1958).

B. OBSTRUCTIVE JAUNDICE

This group is less clearly defined than the non-obstructive group, and is considerably less common. In non-obstructive jaundice the serum bilirubin level is raised as a result of haemolysis or deficient liver-cell function. Neurological damage is not infrequent. In the group with obstructive jaundice there are such obvious conditions as biliary atresia and obstruction of the common bile-duct, but also a number of rather rare conditions which cause severe jaundice and in which the main pigment involved is bilirubin glucuronide. In a

very few instances, however, both types of bile pigment may be present, and if bilirubin should predominate kernicterus can occur. It is, however, extremely rare.

1. Congenital Atresia of the Bile-ducts

This occurs in about 1 in 20,000 deliveries (Moore, 1953). It is the commonest form of neonatal obstructive jaundice. The sex incidence is equal. Moore (1953) found other associated congenital abnormalities in five of his 31 cases, and four of these involved the urinary tract. There are two forms of the condition: (*a*) an extrahepatic atresia, and (*b*) an intrahepatic atresia.

(a) Extrahepatic Atresia

This is more common than the intrahepatic variety. There are many possibilities of maldevelopment of the biliary tree, from a stenosis of the common duct to absence of all extrahepatic biliary structures. The liver is enlarged and a biliary cirrhosis soon develops. On slicing, the cut surface of the organ is seen to be green. Histological examination shows a marked perilobular fibrosis with proliferation of small bile-ducts. The intercellular canaliculi and small bile-ducts contain bile plugs. Some inflammatory-cell infiltration is present in the connective tissue; these cells are mainly lymphocytes and plasma cells. (Special Plate, Fig. 3).

(b) Intrahepatic Atresia

This is exceedingly rare. Curiously enough, it is associated with a longer period of survival than the extrahepatic form (Ahrens *et al.*, 1951; Haas and Dobbs, 1958). The liver is enlarged and green in colour, and it has a finely granular cut surface. The gall-bladder and common duct may be normal. Cirrhosis is a less-marked feature on histological examination. There is some increase in the fibrous tissue of the portal tracts, but no bile-ducts are seen. Bile plugs are present in the intercellular canaliculi.

The skin shows multiple xanthomatous lesions in this form of the disease (Ahrens *et al.*, 1951). In both types of atresia the predominant serum pigment is bilirubin glucuronide.

2. Haemolytic Disease

In a very few cases infants with haemolytic disease remain jaundiced for several weeks. The main pigment in the blood is now found to be bilirubin glucuronide, and apart from the jaundice the infants appear to be well. This is the so-called inspissated-bile syndrome. The liver is enlarged and very firm. The intercellular bile-channels are distended with dark inspissated bile. The portal tracts are normal, as are the main bile-ducts. As a rule the condition clears without treatment, and cirrhosis is almost unknown.

3. Tumour

Very rarely obstructive jaundice may result from the pressure of tumour masses on the common bile-duct. Gross (1953) reported two such cases. In one patient there was a haemangio-endothelioma of the head of the pancreas, and the other had Niemann–Pick disease with enlarged nodes in the gastro-hepatic ligament. Neoplasms of the liver itself are rare in the newborn. The commonest are haemangiomas. These may be exceedingly large, and lead to a fatal haemorrhage if ruptured. The infants may or may not be jaundiced. Very rarely a malignant hepatoma may be found in the neonatal period. These cause great hepatomegaly and metastasize freely. They are associated with jaundice and ascites.

4. Cystic Fibrosis of the Pancreas

Sass-Kortsak *et al.* (1957) have reported a few cases of obstructive jaundice in babies with cystic fibrosis of the pancreas. Focal biliary cirrhosis in a stillborn infant has been described by Claireaux (1956). The lesion tends to be patchy, and in the early stages is mainly subcapsular in situation. In older children this may be followed by widespread hepatic cirrhosis and severe jaundice.

5. Galactosaemia

In severe cases of galactosaemia the infant may be jaundiced shortly after birth. Galactosaemia is a metabolic disorder resulting from a lack of the enzyme capable of converting galactose-1-phosphate to glucose-1-phosphate (Schwarz *et al.*, 1955). The damage to liver and other tissue cells is the result of the toxic action of some metabolite of galactose. In this disease the liver is enlarged and the cut surface has a pale-yellow colour. The liver cells on histological examination show severe fatty change with pronounced vacuolation (Special Plate, Fig. 4). Periportal fibrosis occurs and cirrhosis of the liver develops. The bile canaliculi contain plugs of inspissated bile. Occasional multinuclear giant cells are found. In a few cases liver-cell adenomas develop, and the cells taking part in this formation are full of glycogen (Edmonds *et al.*, 1952). In the untreated patient cataracts may develop after the third week of life.

6. Jaundice in Infection

(a) Bacterial Infection

Jaundice complicating neonatal sepsis is now a rare event. It is only infrequently very pronounced. The liver is enlarged and signs of generalized infection are present. Bilirubin and bilirubin glucuronide levels in the blood are both raised, but the jaundice rapidly disappears if the infection is controlled by the appropriate antibiotics. In a few instances the jaundice results from direct liver damage caused by abscess formation following umbilical sepsis. A rare cause of sepsis giving rise to miliary necrosis of the liver is infection with *Listeria monocytogenes* (Claireaux, Gerrard, and Marsland, 1955).

Severe congenital syphilis is also a rarity in Great Britain, and Nabarro (1954) has expressed some doubt whether it is ever a cause of jaundice in the newborn period. Cases of gross liver enlargement with jaundice previously ascribed to congenital syphilis are probably examples of some other condition. Syphilis can cause a severe intralobular cirrhosis of the liver in the infant, and the histological appearances are highly characteristic (Special Plate, Fig. 5). This may cause jaundice in the older infant.

(b) Viral Infection

(i) *Herpetic Hepatitis.*—A viraemia resulting from infection with herpes simplex virus causes widespread

visceral lesions, including a characteristic focal necrosis of the liver. Jaundice is usually present, but is not necessarily severe. The infant is frequently premature. The liver is enlarged, and multiple white nodules, some of which show umbilication, are raised above the surface of the organ. Similar nodules are seen on the cut surface when the liver is sliced. On histological examination the liver cells in the nodular zones are seen to be necrotic ; those bordering the necrotic areas show nuclear swelling, and eosinophilic inclusion bodies may be present. Similar necrotic areas may be found elsewhere in the body, notably in the brain and suprarenal glands.

(ii) *Congenital Hepatitis.*—The viral nature of this condition is still in some doubt, but the probabilities are in favour of a virus being the aetiological agent. Stokes *et al.* (1951) reported that serum from an infant with hepatitis and from his mother caused hepatitis when injected into volunteers. The incubation period was such that either virus A (infective hepatitis) or virus B (homologous serum jaundice) could be responsible. It would seem unlikely that virus A is the infective agent, as viraemia in this condition is transient and the mother soon develops antibodies to the virus. These strictures do not apply in the case of virus B (Gellis *et al.*, 1954). Smetana and Johnson (1955) believe that the histological appearance of the liver in neonatal hepatitis suggests that the primary lesion is a congenital maldevelopment involving the intercellular bile canaliculi leading from the liver cells to the bile-channels. The " hepatitis " in such an event merely represents the liver cells' response to a variety of stimuli (Bain *et al.*, 1957). Miller (1957) has reported the condition in one of binovular twins. Liver-function tests in the mother would appear to indicate some degree of liver damage, which the author associates with hepatitis. According to Weller *et al.* (1957) the virus of cytomegalic inclusion disease has been recovered from a patient presenting with the signs of a neonatal hepatitis. Obstructive jaundice in 25 patients was studied by Sass-Kortsak *et al.* (1957). Biliary atresia, haemolytic disease, sepsis, and galactosaemia were excluded from their series. They found two examples of fibrocystic disease of the pancreas, and the remaining 23 cases were classified as idiopathic. Some of the idiopathic cases had negative liver-function tests, and the others gave positive results. It was the latter group which were thought to be affected by some virus. Hsia *et al.* (1958) made a new approach to the problem. They conceded that no certain aetiological agent had been demonstrated in neonatal hepatitis ; they therefore investigated the genetic background of 59 families comprising 11 affected and 50 normal siblings. Their statistical data would suggest the theory that the trait responsible for neonatal " hepatitis " is an autosomal recessive. Shorter *et al.* (1959) were also unable to incriminate a single aetiological agent, and suggest that the histological response found in the infant's liver may be to a number of quite different stimuli.

At necropsy the liver may be enlarged, or less frequently it is smaller than usual. The organ is green and the cut surface has a granular appearance. The gall-bladder and main ducts are normal. Histologically, the normal lobular architecture is lost. Numerous exceedingly large multinucleated giant cells are seen (Special Plate, Fig. 6). These cells may have 30 or 40 nuclei. Their cytoplasm has a brownish tinge owing to the deposition of haemosiderin, and the Prussian-blue reaction is positive. Beyond the necrotic areas some islands of regenerating liver cells are found, and these islands may contain haemopoietic foci. There is an increase in fibrous tissue round the necrotic liver cells and in the portal tracts. This connective tissue shows infiltration with lymphocytes and plasma cells. Some proliferation of small bile-channels occurs in the portal tracts, and many contain bile plugs. The origin of the multinuclear giant cells is obscure. Craig and Landing (1952) regarded them as degenerated liver cells fusing to form a syncytial mass. Stokes *et al.* (1951) suggested that they were a response of the liver cell to virus infection, and Dible *et al.* (1954) believed they represented rapid proliferation of liver cells during recovery from the virus infection. If the infant survives beyond the neonatal period a true cirrhosis develops. The infant is jaundiced, and both direct and indirect pigment levels are raised. Kernicterus has been reported in one case by Erhlich and Ratner (1955).

(iii) *Cytomegalic Inclusion Disease.*—Generalized inclusion-body disease is occasionally found in the newborn. The infective agent is said to be salivary-gland virus (Smith, 1956 ; Weller *et al.*, 1957). At necropsy the liver and spleen are found to be enlarged. On histological examination typical inclusion bodies are seen in the epithelial cells of salivary-gland acini, renal tubules, bile-ducts, pancreatic and thyroid acini, and lying free in the lung alveoli. Extramedullary haemopoiesis is marked in the liver if the infant dies shortly after birth. In the older infant these foci disappear. There is some increase in the connective tissue in the portal tracts accompanied by a small bile-duct proliferation. Bile thrombi are present in the canaliculi. The affected bile-duct epithelial cells are greatly enlarged, and contain both intranuclear and cytoplasmic inclusions. The intranuclear inclusion bodies are large acidophilic masses ; cytoplasmic inclusions are small, multiple, and basophilic. They are usually less numerous in the liver than in the kidneys. The infants are jaundiced, and this may become severe. There is an increase in both bilirubin and bilirubin glucuronide in the blood. Kernicterus has occasionally been reported (Kinney, 1942 ; France, 1951).

(c) Protozoal Infection

An acute generalized infection caused by *Toxoplasma gondii* may involve the liver. The infants are jaundiced, and the liver and spleen are enlarged. Calcification of the brain and chorioretinitis are prominent features. On histological examination the liver shows marked erythropoietic activity together with leucocytic infiltration. Histiocytes containing toxoplasma parasites may be present. Bile thrombi are present in the intercellular canaliculi, and the liver cells contain haemosiderin. Areas of necrosis may be present in liver, heart, lungs, and spleen. In these necrotic areas toxoplasma may be found.

KERNICTERUS

The first report of yellow staining of the brain in jaundiced infants is ascribed to Orth (1875). Schmörl (1904) coined the term " kernicterus," and the association with erythroblastosis was soon established. Aiden *et al.* (1950) then reported the occurrence of kernicterus in jaundiced premature infants who did not suffer from haemolytic disease. Similar cases were described by

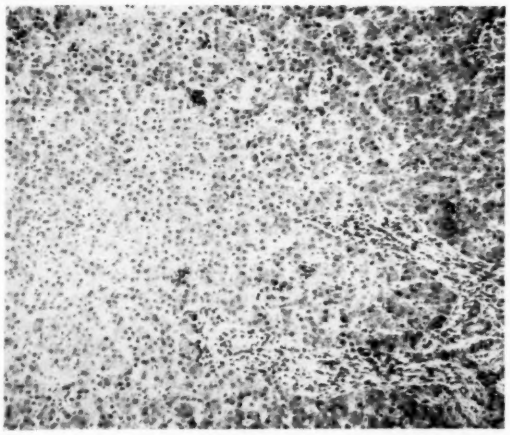


FIG. 1.—Liver. Functional immaturity. No structural defect present, and only an occasional focus of haemopoiesis. (Haematoxylin and eosin. ×60.)

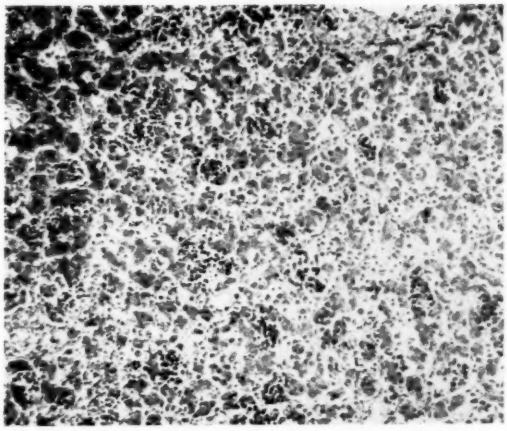


FIG. 2.—Liver. Haemolytic disease. Innumerable haemopoietic foci present. (Haematoxylin and eosin. ×60.)

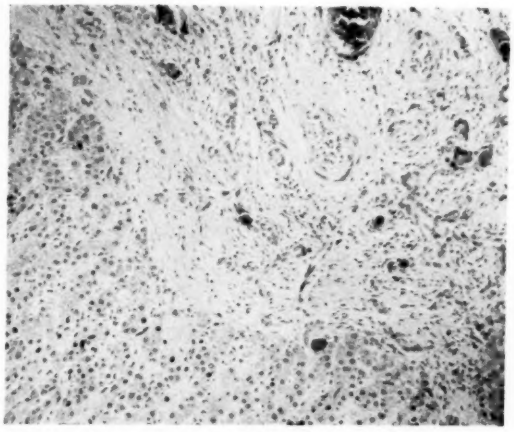


FIG. 3.—Liver. Congenital obliteration of bile-ducts. Increased fibrous tissue in portal tracts. Proliferation of small bile-ducts. Bile-plugs in canaliculi. (Haematoxylin and eosin. ×75.)

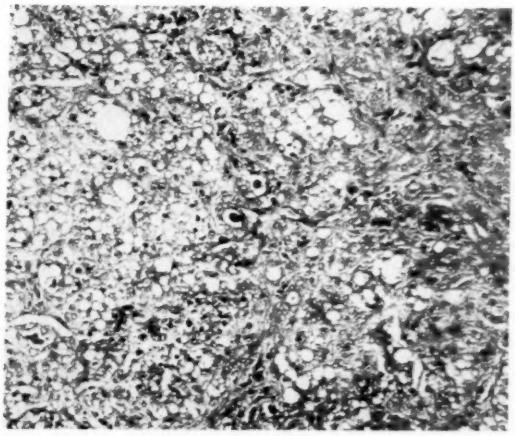


FIG. 4.—Liver. Galactosaemia. (Haematoxylin and eosin. ×90.)

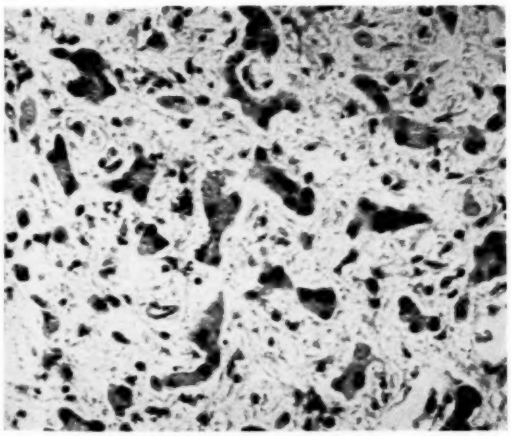


FIG. 5.—Liver. Congenital syphilis. Pericellular intralobular cirrhosis. (Haematoxylin and eosin. ×90.)

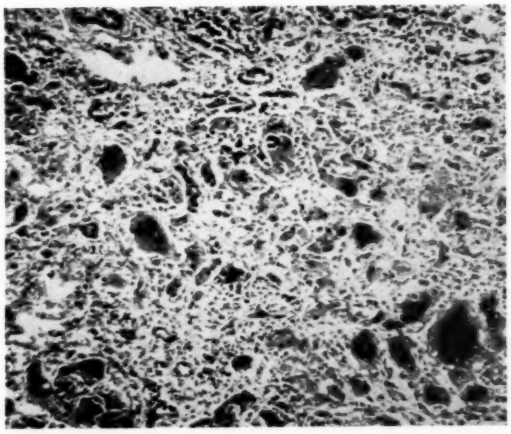


FIG. 6.—Liver. Neonatal hepatitis. Large number of multinucleated giant cells. (Haematoxylin and eosin. ×90.)

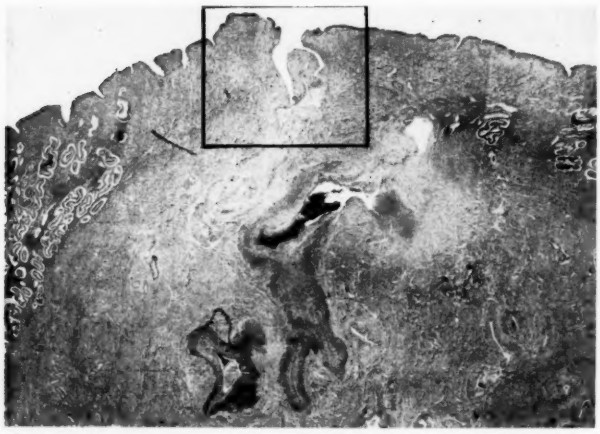


FIG. 1.—Case 1. Low-power view showing myometrium bulging upwards, incorporating large, thick-walled, coiled radial vessel. Aglandular endometrial lining on top. (Haematoxylin and eosin. ×8.)

FIG. 3.—Case 1. Inset of Fig. 1 at higher magnification. Endometrial tear with ruptured endometrial vessel plugged by fibrinous clot. Aglandular endometrium to either side displaying decidual reaction. Beginning epithelization of upper margins of defect. (Haematoxylin and eosin. ×32.)

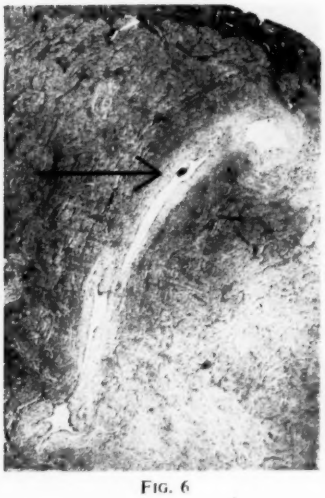


FIG. 6

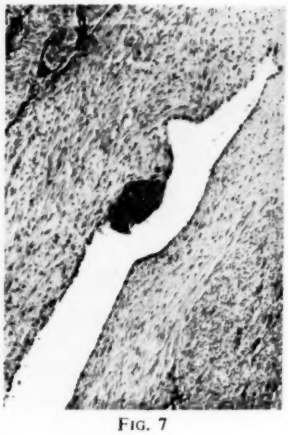


FIG. 7

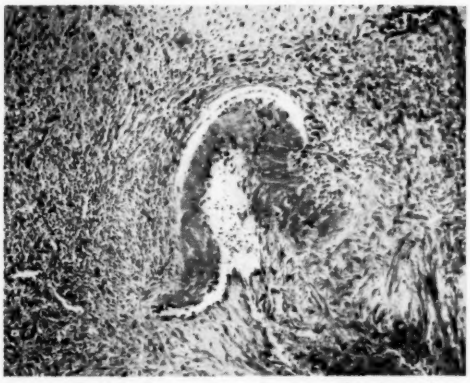


FIG. 2.—Case 1. Ruptured vessel at base of endometrium, surrounded by eosinophil crescent of fibrinoid necrosis. (Haematoxylin and eosin. ×60.)

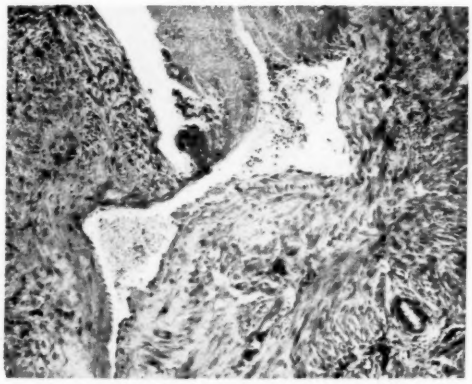


FIG. 4.—Case 1. Detail of ruptured vessel. Fibrin clot at top. (Haematoxylin and eosin. ×60.)

FIG. 5.—Case 2. Low aglandular endometrium in centre with large, thick-walled, distended blood-vessel underneath. (Haematoxylin and eosin. ×24.)

FIG. 6.—Case 2. Low-power view of large-calibre radial myometrial vessel. Myometrium bulging slightly upwards, covered by low endometrium. (Haematoxylin and eosin. ×6.)

FIG. 7.—Case 2. Mural thrombus (arrowed in Fig. 6), partly covered by endothelium, superimposed on thick, fibrous vessel wall. (Haematoxylin and eosin. ×50.)

Zuelzer and Mudgett (1950). Less frequent neurological damage may occur as a sequel to congenital spherocytosis, congenital non-haemolytic jaundice, cytomegalic inclusion disease, or neonatal hepatitis. The association between haemolytic disease and kernicterus was well established, but the risk to the premature infant suffering from "physiological jaundice" was less well known. Meyer (1956) studied the serum bilirubin levels in premature infants with this in mind. He found that in the infant under 2,000 g. birth weight the bilirubin was still rising on the sixth day of life, whereas in the mature infant the peak value was past and the level was falling. He noted that infants with kernicterus had a serum bilirubin level over 18 mg. per 100 ml. A larger group of premature infants was studied by Crosse *et al.* (1958). Of 1,320 premature infants, no fewer than 92 (8.4%) required an exchange transfusion on account of dangerously high levels of bilirubin in the blood. Five of the surviving infants have evidence of neurological damage. These workers found that no infant with a bilirubin level below 20 mg. per 100 ml. developed kernicterus. At levels of 22–27 mg. per 100 ml. the incidence of kernicterus was 19%, and at a level over 30 mg. per 100 ml. it was 33⅓%. Waters (1958) also stressed the danger of allowing the serum bilirubin level to rise above 20 mg. per 100 ml.

It would seem probable, however, that the incidence of very high levels of bilirubin is relatively rare in the premature infant in the absence of a disease process; it probably is not in excess of 1–2% of premature babies under normal conditions. However, it was observed that under certain circumstances the incidence of high serum bilirubin levels would be increased (Laurance, 1955). If excessive doses of vitamin-K analogue ("synkavit") are given, 20–30 mg. daily, then high bilirubin levels and severe jaundice will follow. Asteriadou-Samartzis and Leikin (1958) administered vitamin K to 119 premature infants. Serum bilirubin levels were higher in the infants given vitamin K than in control infants. Vitamin K_1, on the other hand, had little or no effect, nor, it must be emphasized, did vitamin K when given in correct therapeutic dosage. More recently Lucey and Dolan (1959) have reported hyperbilirubinaemia in newborn infants whose respective mothers received vitamin K prior to delivery. In seven cases there was a marked rise in the bilirubin in the first three days of life (20–47 mg. per 100 ml.), and one infant died with kernicterus and one survivor was permanently affected. The authors believe that vitamin K crosses the placental barrier and damages the infant's liver. Gardner (1959) is also of the opinion that vitamin K crosses the placental barrier.

The connexion between very high serum levels of bilirubin and kernicterus, even in the absence of haemolytic disease, was quite obvious, but Silverman *et al.* (1956) reported a number of cases of kernicterus where the serum bilirubin level was only around 15 mg. per 100 ml. They found that their patients had been on a regimen of penicillin and "gantrisin" (sulphafurazole). A further study of the bilirubin levels in infants treated with gantrisin was carried out by Harris *et al.* (1958), and they showed that kernicterus could occur when the bilirubin level was under 15 mg. per 100 ml. A possible explanation for this phenomenon is offered by Odell (1959). It is known that bilirubin is carried on the plasma albumin. If the plasma albumin concentration is low, as in the premature infant, the former becomes readily saturated with bilirubin. If another organic anion is now introduced into the blood which will compete with bilirubin for attachment to albumin, then the amount of *dissociated* bilirubin in the blood will rise. This diffusible unbound bilirubin can attack the cells of the central nervous system. Gantrisin is known to displace albumin-bound bilirubin *in vitro* (Odell, 1958), and apparently will do so *in vivo*. Salicylates are apparently even more effective than the sulphonamides in this respect (Odell, 1959b).

In all the above examples the infants affected by kernicterus have been premature. According to Boon (1957) kernicterus is not uncommon in mature babies in Singapore even if haemolytic disease is excluded. This author ascribes the condition to poor liver function in the infant associated with maternal malnutrition. It may be, however, that some specific factors are involved which are not as yet known.

For many years it was believed that the brain was first damaged by anoxia or other agent, and bilirubin then stained the devitalized tissues. When the nature of the yellow pigment in the brain was demonstrated it was suggested that bilirubin itself was the toxic agent (Claireaux *et al.*, 1953). It is now generally accepted that bilirubin is a highly toxic substance, and one of the effects of its conjugation with glucuronic acid is to render it non-toxic. Ernster *et al.* (1957) have shown that bilirubin inhibits the enzymatic mechanism in brain cells by which phosphorylation is coupled to respiration. They consider that kernicterus is the result of metabolic damage to the central nervous system caused by bilirubin.

The brain is often stained a diffuse yellow colour, especially in the premature infant, but certain nuclear structures are found to be deeply discoloured. The pigmented area may be light yellow or deep orange in colour. The structures most liable to be affected are the corpus striatum (globus pallidus, putamen, lenticular nucleus), thalamus and subthalamic nuclei, hippocampus, nucleus of third cranial nerve, mammillary bodies, red nucleus, nuclei in floor of fourth ventricle, dentate nucleus, flocculus and vermis of cerebellum, and the olives. In some cases the grey matter of the spinal cord and cerebral cortex is also affected. The distribution of lesions varies from case to case, and is generally similar in jaundice caused by functional hepatic immaturity and in haemolytic disease. In the former, however, the yellow staining tends to be slightly paler, and diffuse staining in the region of the periventricular white matter is relatively common. The yellow colour gradually fades if the infant should survive, and in older infants only some slight shrinkage of affected nuclei may be noted at necropsy. On histological examination the brain from an infant dying in the first week of life may show little change. There may be some degree of chromatolysis in the neurones from stained areas, and some of the cells may contain yellow pigment. In older infants there is evidence of marked loss of neurones and replacement gliosis has occurred. Crome (1955) has reported similar changes in the cerebral cortex in patients with mental deficiency following neonatal jaundice.

Neurological damage in infants with severe jaundice in the neonatal period may result in mental deficiency, spasticity, athetosis, or nerve deafness. Modern methods of treatment are directed towards the prevention of such complications.

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INTRACTABLE UTERINE HAEMORRHAGE DUE TO ABNORMAL SUBENDOMETRIAL BLOOD-VESSELS AFTER CHILDBIRTH AND MISCARRIAGE

BY

R. SALM, M.D., L.R.C.P.&S.Ed.
Consultant Pathologist

AND

P. N. SIMONS, F.R.C.S.Ed., M.R.C.O.G.
Consultant Gynaecologist
Camborne–Redruth Hospital, Redruth, Cornwall

[WITH SPECIAL PLATE]

Two cases of severe and intractable menorrhagia in young women are presented which, clinically, were considered to be functional in origin, as no organic cause was clinically demonstrable. Both patients were finally subjected to the drastic procedure of hysterectomy, as every conservative measure taken had failed to stop the recurrent severe uterine haemorrhages. Detailed examination of the operation specimens revealed the presence of large, thick-walled subendometrial blood-vessels, which were interpreted as being normal radial myometrial vessels, probably arteries, which had originally supplied the placental site, had increased in calibre during pregnancy, but had failed to involute during the puerperium. Erosion of these vessels during menstruation we regard as the cause of the exceptionally severe and recurrent menorrhagia—a cause which, to our knowledge, has not been recorded previously.

Case 1

A woman aged 25 was admitted as an emergency on February 15, 1958, because of sudden, severe, painless vaginal haemorrhage on the second day of a period which had began normally. She had two children, the first being born in 1954. A miscarriage, concerning which no details were available, occurred in 1956, and in August, 1957, a normal delivery at home was followed by an uneventful puerperium. A few weeks afterwards she had a heavy period with the passage of clots. A regular 28-day cycle was re-established, but menorrhagia continued and was at times severe.

On examination she showed the clinical signs of acute blood loss. Morphine, 1/4 gr. (6 mg.), was given intramuscularly and 1,600 ml. of whole blood was transfused. When her general condition had improved sufficiently a quantity of blood-clot was removed from the vagina. No abnormality could be found in the cervix, uterine body, and adnexae, nor was there any evidence of systemic disease or blood dyscrasia. A full blood-count gave the following results: haemoglobin, 7.4 g. per 100 ml.; red cells, 2,800,000 per c.mm.; total white cells, 7,700 per c.mm., with polymorphs predominating; platelets, 433,000 per c.mm. Bleeding and clotting times were normal.

Radiological examination of the chest and skull revealed nothing of significance. The urine contained no abnormal constituents, and a male-toad pregnancy test gave a negative result. A curettage was performed, and the histological report on the endometrium proved this to be non-secretory in type. Androgen therapy was instituted, and, no further loss having occurred, she was discharged on February 25, 1958.

On March 17 another severe vaginal haemorrhage on the second day of menstruation led to her urgent readmission. Treatment was by blood transfusion, which had to be twice repeated for intermittent and at times heavy loss. A norethisterone preparation was given, and she was well when discharged on April 21.

Her period in May, 1958, was moderately heavy. In June she was once more admitted as an emergency, again with a history of having had flooding on the second day of the menses. Hystero-salpingography had been attempted twice previously, but free bleeding on the entry of the dye into the uterine cavity had made results inconclusive. When this investigation was repeated as soon as practicable the radiological report was as follows :

> "The cavity of the body of the uterus presents an abnormal contour. The left lateral angle is not present, and this is suggestive of the presence of a filling defect within the cavity, most probably due to a tumour. No contrast medium has entered the left tube."

In view of these findings laparotomy was considered advisable. On opening the abdomen a diffuse fusiform enlargement of the left uterine cornu was noted. Through a longitudinal incision in the anterior surface of the uterus the cavity was opened and searched for a polypus or submucous fibroid, but none was found. It was decided to remove the left uterine cornu together with the corresponding tube, as it was thought that a small tumour at this site might have escaped detection. Histological examination of the excised tissues revealed nothing significant. The post-operative course was smooth and the patient was discharged on the 14th day.

The next haemorrhage was witnessed in the out-patient department in July, 1958. She was waiting to come into the consulting-room, her period having begun two days previously. Without warning a violent vaginal haemorrhage occurred. The blood saturated her clothing, forming a pool on the chair where she had been sitting and a trail on the floor to the examination couch. She was still bleeding when admitted to the ward, and despite massive blood transfusions her general condition steadily deteriorated. It was decided to remove the uterus as an emergency procedure, as this seemed to offer the only hope of saving her life. A total hysterectomy, which she withstood surprisingly well, was therefore performed with all dispatch. A transfusion of 5,600 ml. of whole blood was given before, during, and after operation, and this added to the 4,000 ml. previously transfused gave a total of 9,600 ml. The patient made an uneventful recovery. When last seen, 13 months after hysterectomy, she was very well and showed no evidence of a haemorrhagic diathesis.

Operation Specimen.—The specimen received was a uterus of average size, measuring 9.5×4.5×3.5 cm. and weighing 85 g. The right Fallopian tube was attached and was normal. The cervix measured 3.5 cm. in length and the myometrium 1.8 cm. in diameter. The endometrium was smooth and low. The scar of the previous excision was present at the site of the left cornu. On sagittal slicing a brownish discoloured area of pin-point size was found in the subendometrial myometrium some 2 cm. below the operation scar.

Microscopical Examination (58/1718).—The myometrial scar and the brownish-discoloured area below it were cut in two blocks. The section of the former shows myometrium covered by endometrium of intermenstrual pattern. In the centre of the muscle layer is heavy scarring, incorporating suture material surrounded by a narrow zone of granulation tissue. Below the serosa are ectatic lymph- and blood-vessels and many siderophages. The section from the second shows myometrium covered by endometrium, which is very low in the centre and practically devoid of glands, while its stroma displays, in contrast with the adjacent endometrium, a well-marked decidual reaction, an appearance which is possibly due to marked localized oedema. Here the myometrium bulges upwards in semilunar fashion and contains a single, coiled, large-calibre blood-vessel which runs more or less perpendicularly from the outer myometrium towards the endometrium (Special Plate, Fig. 1). Its thick wall is devoid of muscle and elastic fibres, while its lumen, in spite of an oedematous, proliferated initima, is large and filled with blood. At the endometrial border it gives off some smaller branches, but the main branch continues into the thin, aglandular endometrium just described. Here its wall becomes oedematous, thin, disrupted, and disorganized, while its upper segment is surrounded by a wide crescent of fibrinoid necrosis (Special Plate, Fig. 2), in itself proof of recent extravasation of blood. Further sections cut from this block demonstrate clearly that the wall of this vessel had recently burst, producing a complete breech in the endometrium, though the resulting gap in the endometrium as well as the gap in the vessel wall had already become sealed off and blocked by a comparatively large fibrin–platelet mass (Special Plate, Figs. 3 and 4). The edges of the gap in the endometrium display some epithelization due to downward proliferation of the surface epithelium.

Case 2

A single woman aged 24 was admitted as an emergency on August 11, 1958, because of sudden severe vaginal haemorrhage on the third day of menstruation. In December, 1957, she had a miscarriage at home, and her periods, although regular, had subsequently been heavy and prolonged with premenstrual dysmenorrhoea. On examination she was found to be shocked and collapsed with a weak, rapid pulse and a blood-pressure of 80/40 mm. Hg. Only slight vaginal loss was occurring at this time, and inspection of the cervix showed this to be normal with a little bleeding from the external os. The uterine body was found to be anteverted and a little larger than normal, and both uterine appendages were palpable and somewhat tender. A provisional diagnosis of placental polypus and subacute salpingitis was made. She was given a transfusion of 1,600 ml. of whole blood and intramuscular injections of morphine, 1/4 gr. (16 mg.), and ergometrine, 0.5 mg. When her general condition had improved sufficiently a curettage was performed. Endometrium of non-secretory type was removed, but there were no placental villi. Her post-operative course was uneventful and she was discharged on August 20.

She was urgently readmitted on September 10, 1958, with a history of colicky lower abdominal pain accompanied by the passage of clots per vaginam, estimated as "about a jugful." Her period, which had begun on September 5, had been continuing normally until the sudden onset of pain and haemorrhage a few hours before her admission. When first seen her general condition was satisfactory and bleeding had ceased. No abnormality was found on abdominal or pelvic examination. A full blood-count showed no evidence of blood dyscrasia or defect of coagulation. The haemoglobin level was 10 g. per 100 ml. It was decided to perform a second curettage, as it was thought that a small placental polypus might have been missed previously. On dilating the cervix, blood was seen to be spurting through the internal os, and at the time this was thought to be due to lacerations high in the cervical canal resulting from too rigorous dilatation. No bleeding vessel being visible, the uterine cavity and cervical canal were packed

with gauze. As before, non-secretory endometrium was found on histological examination.

Intermittent bleeding, on the whole not profuse, occurred during the next week and was followed by a sudden severe haemorrhage necessitating the transfusion of 800 ml. of whole blood. Four days later a similar transfusion was required for another heavy loss. She was given a preparation of norethynodrel, and discharged on September 30 with instructions to continue treatment at home.

On November 30, 1958, she was admitted for the third time, again as an emergency and again with heavy loss on the third day of a period. Episodes of severe vaginal bleeding recurred, and she suffered a steady deterioration despite repeated blood transfusions. Total hysterectomy was therefore performed on December 19, from which she made a good recovery. On this occasion 4,000 ml. of whole blood was transfused, and this together with the 3,200 ml. previously administered gave a total of 7,200 ml. The patient, when seen again eight weeks after operation, was in perfect health and there were no signs of a haemorrhagic diathesis.

Operation Specimen.—The specimen was a small uterus measuring 7×4.5×3.5 cm. and weighing 44 g. The cervix measured 2 cm. in length and the myometrium 1.5 cm. in diameter. The endometrium was of average height. On sagittal slicing a tiny brownish-discoloured area was noted situated in the subendometrial myometrium of the lower third of the uterine body.

Microscopical Examination (58/2721).—The entire brownish discoloured area with surrounding tissues was cut by serial step sections in four blocks; the presence of an arterio-venous aneurysm could thereby definitely be excluded. The myometrium, bulging slightly upwards in the centre, is covered by low endometrium of intermenstrual type. In the centre it is very low and practically devoid of glandular tubules (Special Plate, Fig. 5). A large-calibre vessel is coursing in perpendicular fashion through the myometrium towards this area (Special Plate, Fig. 6). It displays a thick, fibrous, oedematous wall which is devoid of elastic fibres and very poor in muscle elements. A short distance below the endometrial border the intimal surface bears several small mural thrombi (Special Plate, Fig. 7) indicative of recent haemorrhage. The outer myometrium contains a vascular plexus and distended capillaries and lymph vessels.

Discussion

It is often difficult to exclude organic disease in cases of functional, or, as some prefer to call it, dysfunctional, uterine haemorrhage. In the cases under discussion a clinical diagnosis was not possible, though every effort was made to establish a basis for effective therapy. As the bleeding followed childbirth in one case and miscarriage in the other, pelvic congestion and infection, placental polypus, subinvolution, and chorion epithelioma were first considered, but later excluded. A physician's advice was asked regarding an underlying systemic cause, but none was discoverable. Possible psychogenic causes were fully considered. The first patient and her husband were interviewed at home in the presence of their family doctor; the second was seen by a psychiatrist while in hospital. The results were of little value.

The cause of the exsanguinating menorrhagia remained unexplained until pathological examination of the excised uteri revealed in both cases the presence of a comparatively large thick-walled blood-vessel coursing in radial fashion from the vascular plexus in the outer myometrium towards the endometrium, giving off smaller branches below it in Case 1, and thus corresponding exactly to the known pattern of the uterine arteries, which have been designated arcuate myometrial, radial myometrial, subendometrial basal, and endometrial coiled arteries respectively. In the present cases, however, these vessels had undergone considerable pathological changes: they were almost totally defective in muscle and elastic fibres, while fibrous tissue and intimal layers had noticeably increased. Thus it was no longer possible to determine histologically whether the abnormal vessels were arterial or venous branches. Considering the rapidity with which each patient became exsanguinated, they may well have been small arteries, but in our opinion this is not of fundamental importance. Whether arterial or venous, the vessel observed in each case was grossly abnormal in comparison with its normal counterpart (see Novak and Novak, 1958).

These abnormal radial myometrial blood-vessels had in both instances been bleeding recently, for which we have adduced histological proof, and we regard them as enlarged, persistent blood-vessels of the placental bed which had failed to involute in the normal way. That such blood-vessels may persist after delivery owing to failure of the physiological process of obliteration has been proved by Rutherford and Hertig (1945). The fact that the severe menstrual bleeding had followed a normal pregnancy in Case 1 and a miscarriage in Case 2 is strong support for this thesis. In each case the uncontrollable bleeding started on the second or third day of the period. It is just about that time that the shedding of the upper endometrial layers would expose these large-calibre, abnormal basal blood-vessels which had been bleeding previously, and any thrombotic occlusion of their stumps could be expected to be removed by fibrinolysis and vascular congestion, thus giving rise to the sudden uterine haemorrhages. This process would be accentuated by the thickened and rigid diseased vessel wall, which almost entirely lacked elastic and muscle fibres, and thus no longer possessed the ability to contract or to be easily compressed by uterine contraction.

The misleading radiological report in Case 1 was most probably due to blood-clot which had accumulated at the site of the bleeding, and was thus responsible for the filling defect observed.

Macroscopically, the site of the bleeding had been characterized in each instance by brownish discoloration which, in conjunction with the clinical history, was so typical that the nature of the lesion was immediately suspected in our second case. It should be noted, however, that the brown colour observed was due to the action of formalin, and not to breakdown products of haemoglobin. In unfixed specimens the colour might be expected to be red.

We do not regard the mechanism recorded in this paper as the explanation of many post-abortal or post-puerperal menorrhagias. On the contrary, on the basis of our experience we regard this as a very infrequent and exceptional occurrence. Moreover, it may well be that in some cases of this type spontaneous cure will eventually result. But we are of the opinion that in a small number of intractable menorrhagias occurring after childbirth or miscarriage the mechanism advanced by us will be found to be the explanation.

Summary

Two cases of recurrent exsanguinating menorrhagia following childbirth and miscarriage, which finally had to be subjected to hysterectomy, are described.

On pathological examination the cause for the severe uterine haemorrhages was found to be a surviving large-calibre vessel of the placental bed, possibly an arterial branch, which had failed to undergo involution in the normal way during the puerperium.

To the authors' knowledge this syndrome has not been described previously.

We would like to express our gratitude to Dr. R. Pollok for allowing us to include his case as Case 2 in this paper, and to Professor R. A. Willis for reading the manuscript. We are indebted to Miss Phyllis E. Coleman for the photography.

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HAEMOGLOBIN "SINGAPORE-BRISTOL"

A "FAST" HAEMOGLOBIN FOUND IN INFANTS

BY

A. B. RAPER, M.D., M.R.C.P.
Royal Infirmary, Bristol

J. A. M. AGER, M.B., B.S.
St. Thomas's Hospital, London

AND

H. LEHMANN, M.D., Sc.D., M.R.C.P., F.R.I.C.
Department of Pathology, St. Bartholomew's Hospital, London

At a symposium on abnormal haemoglobins held in Istanbul in 1957, Fessas (1959a) described a "fast"-moving haemoglobin which he had seen in an infant but not in its parents. The component disappeared from the child's blood when it grew older. This observation was interpreted by Fessas as being possibly the first demonstration of an abnormal foetal haemoglobin. Further details were published by Fessas and Papaspyrou (1957). Also in 1957 Vella (personal communication) noted in Singapore that some cord bloods of Chinese infants contained a fast-moving haemoglobin which could not be demonstrated in the blood of either parent. Early in 1958 he sent specimens to Fessas in Athens and to us in London. Fessas considered that this haemoglobin variant was the same as that which had been seen by him and his colleagues in the Greek infant. At that time Ager and Lehmann (1958) investigated a haemoglobin found in an infant at St. Bartholomew's Hospital. This haemoglobin differed from that sent by Vella and from that described by Fessas and Papaspyrou (1957). It was decided to call this pigment haemoglobin "Bart's," and to refer to the other not yet named abnormal foetal haemoglobin as the "haemoglobin of Fessas and Papaspyrou" ("F & P").

The principal differences between the two haemoglobins were that Bart's moved on paper electrophoresis at alkaline *p*H in front of haemoglobin J, whereas F & P did not, and that Bart's was resistant to alkali denaturation in the "one-minute alkali denaturation test" of Singer, Chernoff, and Singer (1951) and by other alkali-denaturation procedures, whereas F & P was denatured as haemoglobin A.

A difficulty in nomenclature arose in 1958 when Fessas (personal communication) found more cord bloods and bloods of infants with a fast-moving haemoglobin which had all the properties of haemoglobin Bart's, and was led to the conclusion in retrospect that the first example of an abnormal foetal haemoglobin seen by him in 1957 had also been of this type rather than of that which had meanwhile been referred to as F & P. Nevertheless, there existed undoubtedly two types of fast-moving haemoglobins in cord blood of infants whose parents showed no abnormal haemoglobin, one moving on paper electrophoresis at *p*H 8.6 faster and one moving slower than haemoglobin J (Vella, 1959).

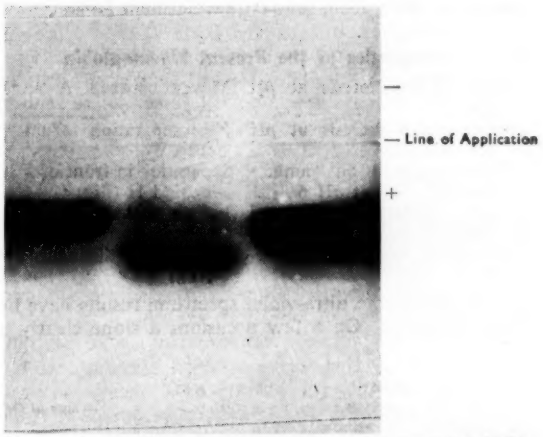

FIG. 1.—Comparison of a haemoglobin A+J control (middle) with the haemoglobins of Case 1 (right) and Case 2 (left). The fast-moving component in Cases 1 and 2 moves slightly less fast than J. Electrophoresis on cellulose acetate with barbiturate buffer *p*H 8.6. Strip stained with light green.

We here record observations on a haemoglobin variant seen in two families in the offspring but not in their parents, which moved on paper electrophoresis at *p*H 8.6 in front of and separating from haemoglobin A but behind the position occupied under this condition by haemoglobin J (Fig. 1).

Case 1.—B.B. presented with anaemia at the age of 2½ years (under the care of Professor C. B. Perry). The spleen could not be felt. The haemoglobin level was 7.4 g./100 ml., and the smear showed considerable hypochromia, anisocytosis, and target cells. There was a satisfactory response to treatment with iron by mouth. The haemoglobin was examined on three occasions, and each time showed a fast-moving component on electrophoresis on paper and cellulose acetate at *p*H 8.6. Alkali-resistant haemoglobin (Singer *et al.*, 1951) 5%. *Family:* Father of French, Portuguese, and East Indian extraction; no haematological abnormality; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 1.7%. Mother English; no haematological abnormality; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 1.7%.

Case 2.—E.T. presented with anaemia at the age of 2½ years (under the care of Dr. J. Apley). The spleen was enlarged three fingerbreadths. Haemoglobin level was 7.4 g./100 ml.; P.C.V., 31.5%; R.B.C., 4,400,000/c.mm.; M.C.V., 72 cubic microns; M.C.H.C., 26%. Serum iron 23 µg./100 ml.; serum bilirubin, 0.35 mg./100 ml. The tibial marrow was normoblastic, with evidence of iron deficiency.

The osmotic fragility of the red cells was normal (a slight "tail" at 0.35 to 0.2% NaCl, presumably due to leptocytosis). There was a satisfactory response to parenteral iron. The haemoglobin was examined on two occasions, and each time showed a fast-moving component on electrophoresis on paper and cellulose acetate at *p*H 8.6. Alkali-resistant haemoglobin 3%, 4%. *Family:* Father of Jamaican origin; his blood was obtained by the kind co-operation of Professor D. V. Hubble, of Birmingham; no haematological abnormality; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 2.1%. Mother English; no haematological abnormality; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 1.9%. Sister by the same father and the same mother, aged 1 year; had a mild microcytic anaemia; haemoglobin level was 11 g./100 ml.; M.C.V., 78 cubic microns; M.C.H.C., 31%; haemoglobin on electrophoresis shows A only; alkali-resistant haemoglobin 3.7%.

Properties of the Present Haemoglobin

Paper electrophoresis at *p*H 8.6	Moves between A and J (Fig. 2)
Paper electrophoresis at *p*H 6.5	No separation from A (Fig. 3)
Chromatography on "amberlite IRC 50" at *p*H 6	Separation in front of F but behind H (Fig. 4)
Alkali resistance of isolated fraction	Indistinguishable from A
Ultra-violet spectrum	Not clearly distinguishable from A

As regards the ultra-violet spectrum, results have not been uniform. On a few occasions a slope clearly of the foetal type was obtained—once on a specimen received from Dr. Vella (Singapore), and once on a specimen from Case 1. However, careful and repeated screening and repetition of ultra-violet spectrum curves failed to yield irrefutable confirmation of the earlier observations, though suggestive results were obtained (Fig. 5). If a foetal type of ultra-violet spectrum exists it must be of a very slight type which cannot be demonstrated with the same ease as that associated with haemoglobin F and haemoglobin Bart's.

The only indication that this variant may be an abnormal foetal haemoglobin is the similarity with haemoglobins F and Bart's, inasmuch as this compound is found in infants but not in parents; but there is no supporting evidence from the results of the alkali denaturation

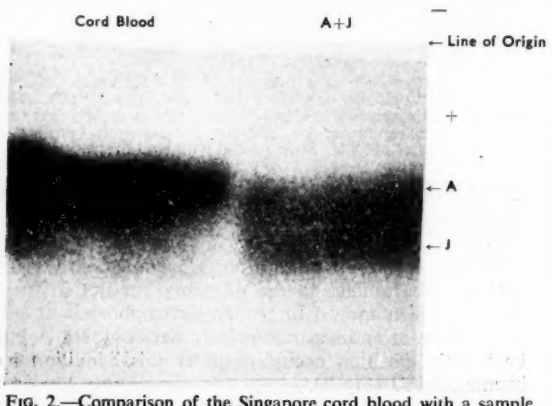

FIG. 2.—Comparison of the Singapore cord blood with a sample of haemoglobin A+J. Paper electrophoresis at *p*H 8.6. Strip unstained. The fast-moving component in the cord blood moves slightly behind J.

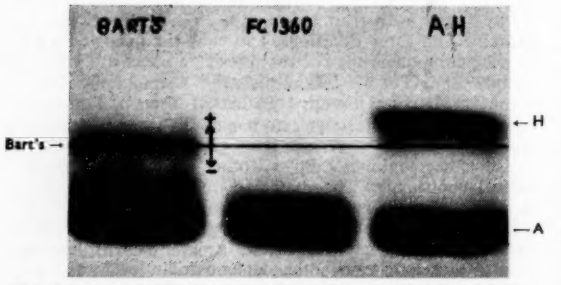

FIG. 3.—Comparison between the cord haemoglobin from Singapore with haemoglobins A+F+Bart's and haemoglobin A+H. Paper electrophoresis *p*H 6.5. Strip unstained. The fast-moving haemoglobin in the Singapore sample does not separate from haemoglobin A.

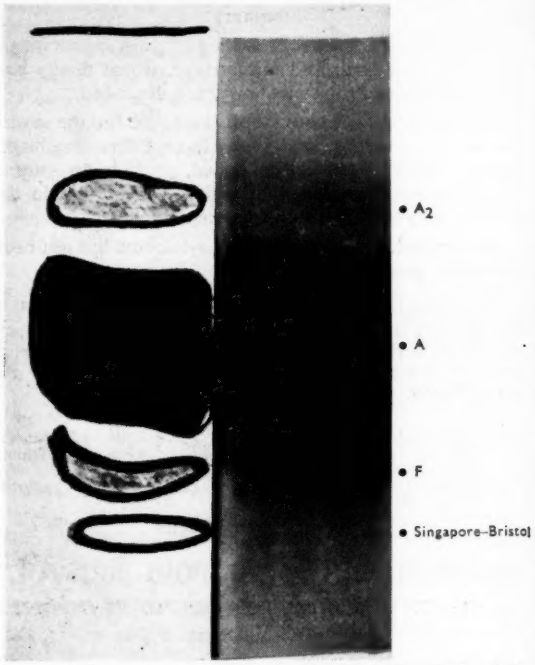

FIG. 4.—Chromatography on amberlite IRC 50, *p*H 6, of the haemoglobin of Case 2. A compound is seen separating in front of the haemoglobin F fraction. The fraction is diffuse and therefore seems to be less in quantity than the F fraction. This is not actually so.

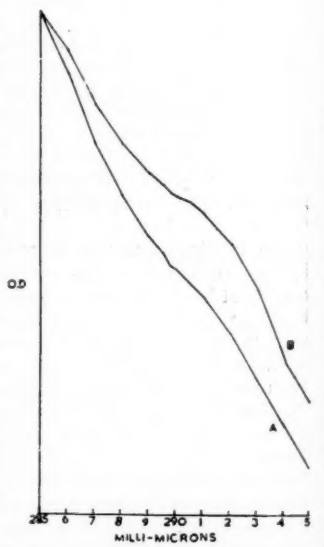

FIG. 5.—Haemoglobin of Case 1. Ultra-violet spectrum of haemoglobin fractions eluted after starch electrophoresis at *p*H 8.6. A = Slow-moving component. B = Fast-moving component (haemoglobin Singapore-Bristol). A slight inflexion at 289.8 mμ; the region of the "foetal notch" is noticeable. This phenomenon was less definite in other samples.

test and the ultra-violet spectrum type which had been so decisive in the case of haemoglobin Bart's.

The variant described here differs from all hitherto described human haemoglobins excepting that observed by Vella (1959) and then referred to as the F & P type. There is even one difference from that described by the Greek authors: the present pigment does not separate from haemoglobin A on acid electrophoresis. Another pigment migrating on alkaline paper electrophoresis behind J and in front of A is haemoglobin K. Haemoglobin K. however, moves slightly slower than the pigment described here and does not separate from haemoglobin A on chromatography. We cannot be sure that the present haemoglobin is truly a variant of haemoglobin F. It could conceivably be a recessive character in the adult series. After consultation with Dr. Vella (Singapore), we have decided on the provisional designation haemoglobin "Singapore—Bristol."

Summary

Of two "fast" haemoglobins seen in infants, but not in their parents, one moves more slowly than haemoglobin J on paper electrophoresis at alkaline *p*H, and the other faster. The second has been described as haemoglobin "Bart's" and is now thought to be the unnamed abnormal foetal haemoglobin seen by Fessas and Papaspyrou in 1957 (Fessas, 1959b). The other moves more slowly than haemoglobin J, and two new examples in infants of mixed marriages are described. This pigment has previously been referred to as the haemoglobin of Fessas and Papaspyrou ("F & P"); it is now redesignated haemoglobin "Singapore-Bristol," and its properties are described.

ADDENDUM.—Two relevant reports have appeared since the above studies were completed. Virginia Minnich and her colleagues (1959) examined the cord blood of 200 infants (110 negroes and 90 Caucasian), and in nine of the negro babies and one of the Caucasians a fast-moving haemoglobin was found which moved more slowly than haemoglobin J on electrophoresis at alkaline *p*H. These authors state that they found this fraction to be relatively resistant to alkali denaturation, whereas we did not find this to be the case for haemoglobin Singapore-Bristol. Hendrickse and his colleagues (1960) found a "fast" haemoglobin fraction in 11% out of 100 cord bloods examined in Nigeria. This fraction persisted for only the first two months of life. Three were examined further, and one of them was found to resemble haemoglobin Bart's and two the haemoglobin described in the present paper.

We thank Dr. F. Vella for discussion and permission to reproduce results obtained with haemoglobin specimens sent to us by him; Professor C. B. Perry and Dr. J. Apley for permission to study their cases; and especially Professor D. V. Hubble for his help in tracing the father in Case 2.

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RESPONSE TO GLUCAGON BY SUBJECTS WITH HYPERINSULINISM FROM ISLET-CELL TUMOURS

BY

VINCENT MARKS, B.M., M.R.C.P.Ed.
Department of Chemical Pathology, Institute of Neurology, National Hospital, Queen Square, London

The isolation and purification (Staub, Sinn, and Behrens, 1955) of glucagon—the hyperglycaemic-glycogenolytic factor—which contaminates many commercial preparations of insulin, enables its effects to be studied in man. Its exact physiological role in intact animals is still in doubt (*Lancet*, 1955; *Brit. med. J.*, 1956), but it is generally agreed that working in conjunction with insulin it facilitates glucose transport from the liver to the peripheral tissues and its utilization there (Anderson, Monaco, Perfetto, and Termine, 1957).

This paper records the results of administering glucagon to four subjects with hyperinsulinism.

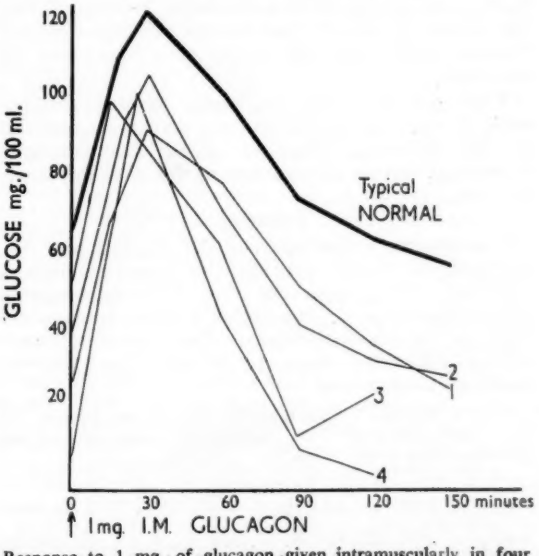
Material and Methods

Glucagon, 1 mg. in 1 ml., was given by intramuscular injection in subjects in the postprandial state, about six to eight hours after the last meal. Glucose concentrations were measured in capillary blood before and at 5, 10, 15, 30, 45, 60, 120, and 150 minutes after the injection by a glucose-oxidase method (Marks, 1959).

Four subjects with organic hypoglycaemia from hyperinsulinism were studied in addition to normal subjects and patients suspected of hypoglycaemia but in whom the diagnosis was not substantiated. In three of the hypoglycaemic patients an islet-cell tumour was removed at operation. The fourth patient refused operation though the diagnosis of insulinism was not in doubt clinically.

Results

The results in normal subjects resemble those observed by others (Hubble, 1955; Alivisatos and



Response to 1 mg. of glucagon given intramuscularly in four subjects with hyperinsulinism from islet-cell tumour. The results from a typical normal individual are shown for comparison.

McCullagh, 1955); there is a rapid rise in blood sugar, about 50–100 mg./100 ml., which reaches a peak within half- to three-quarters of an hour, gradually returning to normal by two hours.

The results in four patients with hyperinsulinism are shown in the Chart. Two had "chemical" hypoglycaemia—that is, blood sugar below 40 mg./100 ml.—prior to the glucagon injection, but only one (Case 4) displayed symptoms. In every case the injection was followed by a rapid rise in blood-sugar, and in the patient with symptomatic hypoglycaemia it was accompanied by clinical improvement. Blood glucose reached a peak by the thirtieth minute and had fallen to, or below, the lower limit of normal by the ninetieth. At two hours severe hypoglycaemic symptoms necessitated termination of the test with glucose in two subjects. In the remaining two subjects hypoglycaemia symptoms appeared between two and two and a half hours; in neither case were they severe, but their hypoglycaemic nature was confirmed by a well-marked clinical improvement with administration of glucose.

Discussion

The response to glucagon administration in patients with hyperinsulinism differs from that observed in healthy subjects by the development of hypoglycaemia after an initial normal hyperglycaemic phase. This characteristic response was observed in all four patients studied and in the one other subject with hyperinsulinism in whom the effects of administering a small dose of glucagon have been published (Alivisatos and McCullagh, 1955). It is not observed in normal subjects under the conditions described: Bondy and Cardillo (1956) gave glucagon by continuous intravenous infusion over a two-hour period and described "hypoglycaemic symptoms" in four subjects; the blood-sugar levels, however, did not fall below 80 mg./100 ml.

A hypoglycaemic phase was not observed to follow glucagon in the two patients with "functional" (reactive) hypoglycaemia studied by Alivisatos and McCullagh. Subjects with liver disease do not show the usual hyperglycaemic response to glucagon (Kibler, Taylor, and Myers, 1952), and it might be expected that this would be equally true in cases of hepatogenous hypoglycaemia; but more information is required on this point.

Thus glucagon may be useful in distinguishing subjects with hyperinsulinism from normal subjects and in the differential diagnosis of the hypoglycaemic syndrome; further investigation in this direction seems justified.

Summary

The response to the intramuscular injection of 1 mg. of glucagon in four patients with hyperinsulinism is recorded. A hypoglycaemic phase following a normal rise in blood sugar distinguishes it from the response observed in healthy subjects. The use of glucagon in the differential diagnosis of the hyperglycaemic syndrome is discussed.

It is a pleasure to acknowledge the gift by Messrs. Eli Lilly and Company Ltd., Basingstoke, England, of the glucagon used in this work.

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SERUM TRANSAMINASE IN ENDOMYOCARDIAL FIBROSIS

BY

JEAN CAMPBELL, B.Sc.
Biochemist, Uganda Medical Department

AND

K. SOMERS, M.B., M.R.C.P.
Lecturer in Medicine, Makerere College Medical School, Kampala, Uganda

The pathology of endomyocardial fibrosis essentially consists of fibrosis of the ventricular cavity endocardium and of the underlying myocardium, usually around the region of the apex. Extension of the lesion may sometimes involve the atrio-ventricular valves. Histologically, acute necrosis of myocardial fibres has not been seen (Davies and Ball, 1955). The usual presentation is the clinical picture of congestive cardiac failure, often with evidence of pure mitral and/or tricuspid incompetence, but it often presents as heart failure without other distinguishing features (Ball *et al.*, 1954). Despite the recognition of a suggestive electrocardiographic pattern (Williams and Somers, 1960), and characteristic phonocardiographic signs (Somers and Williams, 1960), an exact diagnosis of the syndromes of endomyocardial fibrosis is difficult and can be confirmed only at necropsy. LaDue *et al.* (1954) first reported the elevation of the serum glutamic oxalacetic transaminase (G.O.T.) after necrosis of cardiac muscle in man. Agress *et al.* (1955) found from experimentally produced myocardial infarction in dogs that the increase of serum G.O.T. was proportional to the amount of infarction estimated at necropsy. Serial estimations of serum G.O.T. and other enzymes assist in the diagnosis of myocardial infarction where electrocardiographic and other diagnostic features are atypical or doubtful (Kattus *et al.*, 1957; Baron *et al.*, 1958; Dewar *et al.*, 1958; Sampson, 1958; Goble and O'Brien, 1958; Keele *et al.*, 1958).

The object of the present study was to assess the value, if any, of estimations of serum G.O.T., which we shall refer to simply as transaminase, in endomyocardial fibrosis.

Material and Methods

Serum transaminase activity was estimated in a series of 24 patients admitted to Mulago Hospital during the first six months of 1959. There were 12 males and 12 females. Their ages ranged from 12 to 55 years. All the patients were in congestive heart failure when the first estimation was made. Subsequent estimations were carried out in various stages of recovery. In seven patients serum transaminase was estimated for periods exceeding two weeks. The investigation was done in patients with suspected endomyocardial fibrosis in whom the problem of diagnosis from hypertensive heart disease, heart failure due to severe anaemia, aortic valve disease, and other conditions was excluded on clinical findings. The diagnosis of endomyocardial fibrosis was based on clinical evidence of pure atrio-ventricular incompetence —mitral, tricuspid, or both—or heart failure and triple

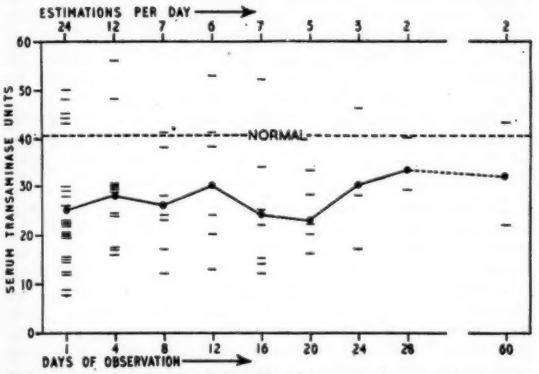
rhythm of apparently obscure origin associated with suggestive electrocardiographic signs.

Mid-morning specimens of blood were taken twice weekly.

The method of Reitman and Frankel (1957) was used throughout. Dr. J. H. Wilkinson, of Westminster Medical School, London, kindly agreed to duplicate tests using the spectrophotometric method (Karmen, 1955) on refrigerated serum sent to London by air. Duplication was good. Repeat estimations on the same serum kept in the "deep freeze" for up to seven days made no difference to the results.

Results

A total of 68 transaminase estimations were carried out on 24 patients. Of these all but 13 were within the normal range. Any variation appeared to be



Scatter of transaminase levels and the mean values in 24 patients with endomyocardial fibrosis.

completely random. No significant trend was found. The mean serum transaminase value was 25.8 units. The range was 8 to 57. Serial mean values were at the upper range of the accepted normal. Serum transaminase did not vary significantly from estimation to estimation in serial readings in the same patient. The Chart shows the scatter of serum transaminase levels and the mean value of serial estimations over 28 days under observation.

Discussion

The pathology of endomyocardial fibrosis is characteristically a fibrotic process. By the time the clinical syndromes are recognizable, fibrosis is usually an established lesion. The process of myocardial degeneration and fibrosis is probably gradual enough to cause little rise in serum transaminase levels.

Single specimens of serum show a transaminase value within the normal range. Repeated examinations show no significant changes in values. In patients in whom a clinical diagnosis of endomyocardial fibrosis is suspected, serum transaminase estimations appear to offer no objective help in the confirmation of diagnosis. Short of an ability to recognize an "acute phase" of endomyocardial fibrosis with true cardiac-muscle necrosis, serial estimations of serum transaminase are unlikely to help in diagnosis. Liver disease may show high transaminase values. Hepatocellular damage is not usually a diagnostic problem in heart disease, but congestive failure can produce high transaminase levels through damage to the liver (Sampson, 1958). The high normal values in some of our patients are probably explained by the same concept.

Summary

In the light of our present experience we do not consider estimation of serum transaminase a diagnostic aid in established endomyocardial fibrosis.

In the clinical syndromes of endomyocardial fibrosis the serum transaminase levels are usually within the normal range. The reasons for this are discussed. Serum transaminase may have diagnostic value in an "acute phase" of endomyocardial fibrosis, but such a lesion has yet to be recognized.

We thank Dr. J. H. Wilkinson and Miss Celia Matthew for running parallel tests. We are grateful to Professor J. N. P. Davies, Dr. Francis Lothe, and Dr. F. L. Mitchell for encouragement, and to Mr. R. Gichuru Gitau for help with the collection of specimens. We also thank our patients for enabling the investigations to be done, and the Director of Medical Services, Uganda, for permission to publish.

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The South Pacific Commission is an advisory and consultative body set up by the Governments of Australia, France, the Netherlands, New Zealand, the United States of America, and the United Kingdom on February 6, 1947. The territories with which the Commission is concerned lie roughly between the Tropic of Cancer and the Tropic of Capricorn, extending from French Oceania in the east to Netherlands New Guinea in the west, and from the Marianas, Guam, the Carolines, and Marshalls in the north to the Cook Islands and New Caledonia in the south—an area of about twelve million square miles or approximately four times that of Australia. The islands are inhabited by over three million people. The Commission appointed a Research Council whose principal duty is to maintain a continuous survey of research needs in the territories, to make recommendations to the Commission on research to be undertaken, to arrange with the Secretary-General for the carrying out of research projects approved by the Commission, and to co-ordinate the research activities of other bodies working within the area. The Commission's programme covers health and socio-economic development, and for the past three years it has operated a very useful health education training course for members of the medical, nursing, and education service, and has published material on public-health subjects of importance to workers and to the community. Mosquito-borne diseases have received special attention, particularly filariasis, which is the cause of widespread ill-health. The Commission has been responsible for important field and laboratory studies on food and diet in relation to nutrition, and has applied the knowledge to problems of cultivation and distribution, including the introduction of fishponds. Tuberculosis provides a difficult problem, and was the subject of a special conference in 1954 in Samoa. The headquarters of the Commission are at Noumea, New Caledonia, with a branch office in Sydney.

LOWER-LIMB PAIN IN CHRONIC RUPTURE OF ABDOMINAL ANEURYSMS

BY

C. R. SAVAGE, M.B., F.R.C.S.

AND

E. J. GALLAGHER, M.B., B.S., F.R.C.S.I.

South Warwickshire Group of Hospitals

The common methods of presentation of aneurysms of the aorta and common iliac artery are well known (Barratt-Boyes, 1957). They may be discovered accidentally at examination or at operation for some unrelated condition. They may present as abdominal swellings noticed by the patient or give rise to symptoms due to pressure on surrounding structures; of particular importance is the presence of abdominal pain radiating through to the back, or back pain alone may occur.

When acute rupture takes place abdominal pain is severe and there is the picture of an acute abdominal emergency with signs of shock, internal haemorrhage, and an enlarging tender abdominal swelling, usually more pronounced on the left side. Aneurysmal rupture may, however, be subacute or chronic for a considerable period before the acute episode of haemorrhage occurs and may then give rise to misleading symptoms. The following three cases—two of aortic and one of common iliac artery aneurysm—all presented with pain referred to the lower limb and were treated under the impression that this was due to a skeletal cause, until sudden acute on chronic rupture of the sac, accompanied for the first time by abdominal pain, revealed their true nature.

Case 1

A man aged 64 was admitted to hospital under the care of one of us (E. J. G.) on June 10, 1959, complaining of having had pain in the region of the left hip for three weeks. The pain was severe and radiated down the leg, and there was little relief on resting. He had suffered from tuberculosis of the right hip in 1915, and this was followed by ankylosis of the joint and some shortening of the leg. His previous health had been otherwise good.

Examination showed limitation of movements of the left hip in all directions and diminution of the left knee-jerk. Both ankle-jerks were normal and the plantar reflexes were flexor. The pulses in the legs were normal. *X*-ray examination of the left hip-joint showed no abnormality, that of the lumbar spine spondylosis only, and the chest was clear. Treatment with "butazolidin" and traction produced some temporary relief in severity of the pain. In the next few weeks increasing weakness of the left quadriceps muscle developed with some wasting. The left knee-jerk was obtained only with reinforcement, and there was sensory loss over the inner side of the thigh. A myelogram on July 30 showed no abnormality. A neurological opinion arising from this investigation confirmed the presence of an L 3 root pressure syndrome, and exploratory laminectomy was advised with a tentative diagnosis of neurofibroma or secondary carcinoma. This was carried out on August 25 (E. J. G.).

The spinal canal from L 1 to L 4 was exposed but no abnormality was discovered. There was no evidence of vertebral disk prolapse and exploration of disk spaces was not carried out. Post-operative progress, apart from continued pain in the left hip, was satisfactory until September 6, when pain spread to the left side of the abdomen. Examination at this time showed a hard, tender mass in this region which was pulsatile. The pulsation was thought to be transmitted and not expansile. Pain became more severe and the swelling larger during the next 24 hours, with a rising pulse rate and evidence of continuing internal haemorrhage and swelling of the left leg due to pressure on the left iliac vein.

A diagnosis of ruptured aortic aneurysm was made and operation was carried out on September 7 (C. R. S) after further blood transfusion. This confirmed the presence of a large retroperitoneal haematoma resulting from acute on chronic rupture of an abdominal aortic aneurysm; active bleeding and both old and recent clot were present. Resection of the aneurysm was performed, followed by the insertion of a Teflon bifurcation graft. Recovery from operation was satisfactory except for a temporary oliguria in the early period (maximum blood urea 134 mg./100 ml.) which responded to standard treatment.

Case 2

A male aged 76 was admitted on May 4, 1959, with severe abdominal pain of about 10 hours' duration. The pain was most severe in the right lower quadrant, but the history was difficult to obtain owing to his extremely shocked condition. He had been attending the hospital orthopaedic department for the previous month as an out-patient for treatment of pain in the right hip and thigh, of three months' duration, accompanied by paraesthesia, pain on straight-leg raising, and diminution of the ankle-jerk. There had been some slight improvement in his symptoms immediately preceding the acute onset of abdominal pain.

Examination on admission showed him to be extremely pale, shocked, and cold; temperature 96.4° F. (35.8° C.), pulse 86, respirations 24, blood-pressure 80/60. There was marked guarding, rigidity, and tenderness in the right lower quadrant of the abdomen, where a large swelling was present. Pulsation was not detected. Both femoral pulses were present. A diagnosis of ruptured abdominal aneurysm was made. Intensive treatment for shock and haemorrhage was carried out in the course of the next few hours. Despite replacement of blood loss—9 pints (5.1 litres)—his condition failed to improve and his blood-pressure fell to 70/50. It was felt, nevertheless, that surgical treatment offered the only chance of survival. Before this could be carried out, however, he collapsed and died five hours after admission to hospital. Necropsy confirmed the presence of a large ruptured abdominal aneurysm with an enormous retroperitoneal haematoma, most pronounced on the right side.

Case 3

A man aged 28 was admitted on July 19, 1957, under the care of Dr. S. Whittaker with a three-weeks history of pain in the left leg starting at the knee and later involving the thigh and hip region. For two weeks he had also noticed numbness in the left foot which had gradually extended up the leg. Treatment had been carried out by his family doctor with bed rest, radiant heat, and analgesics, but there had been no significant relief. The pain had become more severe the day before admission. He had been blind since the age of 18 years, when he had been found to be suffering from Behcet's syndrome. His health had otherwise been good.

On examination his temperature was 101.4° F. (38.6° C.), pulse 114, and blood-pressure 140/80. He was not clinically anaemic. Heart and chest showed no abnormality. Positive findings were flexion of the left knee and hip with obvious pain in these regions. Spasms of more severe pain occurred at intervals, and appeared to be unrelated to movement. Limitation of movements in the left hip-joint was present and straight-leg raising caused pain in the flexor muscles of the thigh. Reflexes in the legs were normal, but there was some sensory loss to pin-prick extending up the inner side of the left leg from the ankle to the mid-thigh. There was slight diminution of vibration sense on the same side. Tenderness was present in the left iliac fossa but no swelling was felt. Pulses in the legs were present and equal on both sides. Investigations: haemoglobin, 11 g./100 ml.; W.B.C., 20,600/c.mm. (polymorphs, 74%). *X*-ray films of the chest

showed nothing abnormal, and those of the pelvis were unsatisfactory owing to flexion of the hip causing technical difficulties.

Symptomatic treatment was given, and on July 20 his condition was unaltered. On July 21 the pain in his left hip became much more severe and spread to the left side of his abdomen. He was found to be pale, cold, and sweating, with a subnormal temperature and raised pulse rate. There was marked guarding in the left iliac fossa, and a large tender non-pulsatile swelling was felt. The signs in the left leg, apart from increased flexion of the hip, were as before. A diagnosis of retroperitoneal haemorrhage was made.

After blood replacement, operation was carried out by one of us (C. R. S.) the same day (July 21). This confirmed the presence of a large retroperitoneal haematoma on the left side with a small quantity of blood in the peritoneal cavity. Both recent and old blood-clot were present and there was gross disruption of the psoas muscle and retroperitoneal tissues. The aorta and iliac arteries appeared normal and bleeding had ceased. The left kidney was also normal. Despite a careful search the source of bleeding was not discovered and the wound was closed, with drainage. Five hours after operation renewed bleeding occurred through the drain site: this was controlled by blood replacement. The next day, however, a further massive haemorrhage took place, and, despite blood transfusion, he died later the same day. Necropsy revealed a ruptured aneurysm about 1 cm. in diameter arising from behind the bifurcation of the left common iliac artery. It was thought to be of congenital origin, as there was no evidence of arteriosclerosis.

Discussion

Bonney (1956) and Filtzer and Bahnson (1959) have drawn attention to the occurrence of pain in the back and lower limb in occlusive disease of the aorto-iliac arteries and have stressed the importance in diagnosis of a history of its relation to exercise and the necessity for routine palpation of the femoral arteries. That pain may be referred to the lower limb from leaking aorto-iliac aneurysms is less well known, and the diagnosis of such cases may be extremely difficult. A history of claudication is likely to be absent and the femoral pulses will probably be normal. Early recognition is of great importance, and may be assisted by attention to the following points. The distribution of referred pain in leaking aneurysm is likely to differ from that of the usual sciatic-nerve-root-pressure syndromes, and it is unlikely to be relieved by the standard conservative measures used in the treatment of these conditions. Careful abdominal palpation should be added to the routine examination of cases of backache and lower-limb pain and may reveal an abdominal swelling which may be pulsatile. The presence of obesity can, however, result in even large swellings in the retroperitoneum being overlooked. Radiography of the abdomen will show calcification in the wall of aneurysms in a small proportion of cases, but erosion of the vertebral bodies is rarely seen.

Summary

Three cases of referred pain in the lower limb due to chronic rupture of aortic and iliac aneurysms are described. The difficulty in diagnosis is stressed, and the necessity for consideration to be given to the condition as a cause for atypical " sciatic " root pain is emphasized.

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CARCINOMA OF THE BRONCHUS PRESENTING WITH GASTRO-INTESTINAL SYMPTOMS

BY

E. J. M. WEAVER,* F.R.C.S.

AND

R. H. BALME, D.M., M.R.C.P.

The London Hospital

The object of this paper is to draw attention to the fact that carcinoma of the bronchus may present with gastro-intestinal symptoms.

In the terminal stages of any fatal illness the patient may suffer from gastro-intestinal disturbances, and in such circumstances they give rise to no great diagnostic difficulty. When, however, abdominal symptoms are the first indication of a serious respiratory disease, it is vital that their significance should not be overlooked. A series of cases of carcinoma of the bronchus is presented illustrating this point.

Material

In the period June, 1956, to July, 1958, out of 333 patients with carcinoma of the bronchus admitted to the department of thoracic surgery at the London Hospital, 17 presented with gastro-intestinal symptoms. In no instance was there evidence of intra-abdominal metastases on clinical examination. In 13 cases the growth was resected either by pneumonectomy or by lobectomy. Of the remaining four, two were found to have irremovable lesions at thoracotomy, and two were not subjected to surgery, spinal metastases being present in one and pleural involvement, proved by needle biopsy, in the other.

The patients can be divided into two groups. Group 1 consists of five cases which on investigation were shown to have ulceration of the stomach or of the duodenum, as well as a carcinoma of the bronchus. Group 2 consists of 12 cases in which no peptic ulceration was demonstrated, the bronchial lesion alone being held responsible for the abdominal symptoms.

Four case-histories are given to illustrate the type of clinical presentation encountered. The Table gives details of all the cases.

Case Reports

Case 1.—Six months prior to admission, a man aged 55 developed symptoms of vomiting after meals associated with epigastric pain which was relieved by alkalis. He had had no previous gastric symptoms, but was accustomed to smoking 25 cigarettes a day. One month prior to admission, a barium-meal examination showed the presence of a duodenal ulcer for which conservative treatment was advised. His vomiting became so severe that he had to be admitted to hospital, and an *x*-ray film of the chest taken at that time showed a lesion in the left lower lobe. At operation a carcinoma was found arising in the apical segment of the lower lobe and spreading on to the left main bronchus to involve the vagus nerve below the origin of the recurrent laryngeal branch. A pneumonectomy was performed. After operation the patient had no further symptoms referable to the duodenal ulcer, though no other treatment was given.

Case 3.—Two months prior to admission, a man aged 63 developed symptoms of flatulence and epigastric pain one

*Now at University College Hospital, Ibadan, Nigeria.

Details of Cases

Case No.	Age and Sex	Duration of Gastric Symptoms Prior to Diagnosis of Carcinoma Lung	Past History	Cigarette Consumption	Gastro-intestinal Lesion	Chest X-ray (Position of N.G.)	Treatment	Vagus Nerve Involvement
1	55 M	6 months	Nil relevant	25/day	D.U.	L.L.L.	Pneumonectomy	Proved
2	59 M	14 ,,	Perforated D.U. at onset of symptoms	20/day	,,	R.U.L.	,,	Unproved
3	63 M	2 ,,	Perforated D.U. 16 years ago	30/day	Scarring of duodenal cap	* L.L.L.	Lobectomy	,,
4	44 M	18 ,,	Nil relevant	15/day	G.U.	R.U.L.	Pneumonectomy	Proved
5	55 M	1 month	,, ,,	40/day	,,	,,	,,	,,
6	65 M	4½ months	Cholecystectomy 6 years ago	20/day		L.L.L.	,,	,,
7	67 F	3 ,,	Nil relevant	10/day		,,	Thoracotomy	,,
8	60 M	14 ,,	,, ,,	70/day. Non-smoker for last 5 years		L.U.L.	Pneumonectomy	,,
9	50 M	4 ,,	Vomiting and epigastric pain 12 years ago	20/day	Laparotomy 3/52 prior to chest op. No peptic ulcer	L.L.L.	,,	,,
10	45 F	6 years	Nil relevant	30/day	Two barium meals in 6 years. Both negative	L.U.L. Spinal metastases		L. recurrent laryngeal nerve involved
11	56 M	5 months	G.U. 10 years ago	30/day		R.U.L.	Thoracotomy	Unproved
12	58 M	4 ,,	Nil relevant	20/day. Non-smoker for last 3 years		,,	Lobectomy	Proved
13	60 M	1 week	Ba meal=G.U. 20 years ago	40/day		R.L.L.	,,	Unproved
14	53 M	5 months	Nil relevant	15/day		L.L.L.	,,	,,
15	46 F	15 ,,	,, ,,	30/day		R.L.L.	Pleural biopsy	,,
16	56 M	3 weeks	D.U. 6 years ago	40/day		,,	Lobectomy	Proved
17	72 M	7 months	Nil relevant	15/day		R.U.L.	,,	Unproved

hour after meals which was relieved by alkalis. Twenty-five years ago a duodenal ulcer had been diagnosed, and 16 years ago it had perforated. After suturing of the perforation he had remained symptom-free until his present illness, in spite of the fact that he had continued to smoke 30 cigarettes a day. A barium-meal examination showed scarring of the duodenum but no evidence of active ulceration. A chest *x*-ray film revealed a mass in the apical segment of the left lower lobe. At operation a carcinoma was found arising in the apical segment of the lower lobe, which was removed by lobectomy. After operation he had no recurrence of his gastric symptoms up to the time of his death from distant metastases four months later.

Case 7.—Three months before admission, a woman aged 67 developed symptoms of nausea, vomiting, and distaste for fatty foods. She was investigated as an out-patient. A barium-meal examination and cholecystogram were negative. Six weeks after the onset these symptoms disappeared. In the month preceding admission she developed a cough and shortness of breath. A chest *x*-ray film showed a collapsed left lower lobe, and she was referred for thoracic surgical opinion. At operation a carcinoma was found arising in the lower lobe, invading the left auricle near the inferior pulmonary vein. At that level the oesophagus and left vagus were surrounded by growth. The carcinoma was regarded as irremovable.

Case 9.—Four months prior to admission, a man aged 50 developed symptoms of vomiting and pain two hours after meals. Twelve years previously he had had similar symptoms, but a barium-meal examination at that time had shown no abnormality. During the recent attack no ulcer was demonstrated, but the patient's symptoms were so severe that a laparotomy was performed. The stomach and duodenum were found to be normal. A post-operative chest *x*-ray film revealed a lesion in the apical segment of the left lower lobe, and the patient was transferred to the thoracic surgical unit. At operation a carcinoma was found arising in the left lower lobe, extending across the fissure into the upper lobe. The left vagus nerve was surrounded by growth at the level of the inferior pulmonary vein. A pneumonectomy was performed, and after operation the patient had no recurrence of his gastric symptoms.

Discussion

Philip (1824) and Hutchinson (1855) described dyspepsia in phthisis and the association of peptic ulcer with chronic bronchitis has also been described (Jones, 1957), but the coexistence of bronchial carcinoma with peptic ulcer in the same patient has not been the subject of comment. Since both peptic ulcer and bronchial carcinoma are very common, especially in middle-aged men who smoke cigarettes, the two conditions will often occur together by chance. It would be wrong to conclude from our material that bronchial carcinoma was more common in patients with peptic ulcer than in others.

Our 17 cases represent 5% of all those admitted to the department of thoracic surgery for bronchial carcinoma during a two-year period. According to Doll and Jones (1951), about 6% of working-men aged 45–64 years had symptoms of active peptic ulcer during the year preceding interview, and "non-ulcer dyspepsia" was much more common.

On the other hand, in all our cases there was a relationship in time between the onset or exacerbation of gastro-intestinal symptoms and the diagnosis of bronchial carcinoma. Abdominal symptoms preceded the respiratory symptoms by weeks or months, and we believe that the gastro-intestinal disorder was provoked or exacerbated by the pulmonary lesion. Though all our patients had been heavy smokers, this could not have been responsible for the abdominal symptoms in at least two patients who had ceased to smoke five and two years respectively before the onset.

Any respiratory disease may be associated with gastric symptoms if infected sputum is swallowed, if there is anoxaemia or carbon-dioxide retention, or if irritant expectorants and adrenergic drugs are taken. In our patients, however, none of these factors could have been responsible, since gastro-intestinal symptoms occurred before respiratory function was significantly disturbed and often in the absence of cough or sputum. A small primary carcinoma may influence distant organs by the release into the blood-stream of some active principle or by removing some essential nutrient. Such a humoral mechanism must operate to produce systemic effects like anaemia (when not due to loss of blood), cachexia,

FIG. 1.—Case 1.—Carcinoma arising in the apical segment of the lower lobe, extending on to the left main bronchus, and surrounding the vagus nerve.

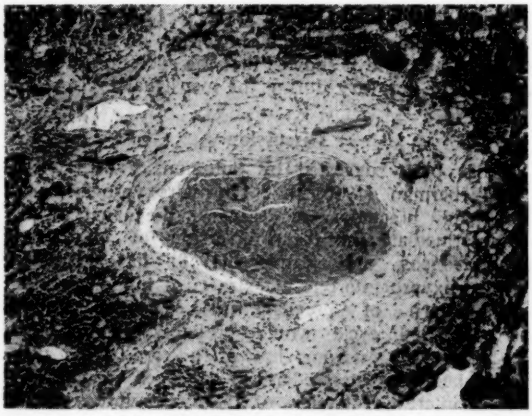

FIG. 2.—Case 1. Photomicrograph showing the vagus nerve surrounded but not invaded by growth.

fever, neuropathy, myopathy, and migrating thrombophlebitis. We cannot rule out the possibility that a humoral mechanism was responsible for gastro-intestinal symptoms in some of our cases. On the other hand, in nine instances the vagus nerve was surrounded by the growth though the nerve was never actually invaded (see Figs. 1 and 2). In these cases (and perhaps in others) the vagus may have been chronically irritated by compression. After prolonged irritation the nerve might become tolerant to compression or even be paralysed. This could be one reason for the cessation of abdominal symptoms before operation.

Gastric hypersecretion, hypermotility, and acute erosions can be produced in animals by stimulation of one vagus nerve (Talma, 1890). Focal haemorrhagic erosions and ischaemic lesions have been observed repeatedly after chronic vagal stimulation, though chronic peptic ulcer has not been produced experimentally in this way (Ivy, Grossman, and Bachrach, 1950). In men, peptic ulcer may be associated with various intracranial lesions (Cushing, 1932), and the neurogenic theory of duodenal ulcer was based largely on the concept of continuous vagal overactivity. Whatever reservations one may have about the validity of this theory, it must be admitted that chronic vagal irritation would be expected to produce gastro-intestinal symptoms and possibly peptic ulceration.

Whatever the mechanism involved, the coexistence of bronchial carcinoma and dyspepsia poses a diagnostic problem. Error is particularly likely when the only symptoms are gastro-intestinal, a peptic ulcer is demonstrated, and routine chest *x*-ray examination shows minimal changes of doubtful significance.

Summary

Seventeen cases of bronchial carcinoma presenting with gastro-intestinal symptoms are reported.

It is suggested that irritation of one of the vagus nerves by the growth in the thorax may be responsible for the production of symptoms.

We thank Mr. Vernon Thompson and Mr. Geoffrey Flavell for permission to report these cases and for their advice, and Professor Clifford Wilson for helpful criticism.

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EXCRETION OF PREGNANETRIOL DURING THE NORMAL MENSTRUAL CYCLE

BY

K. FOTHERBY, Ph.D., B.Sc.

Clinical Endocrinology Research Unit (Medical Research Council), University of Edinburgh

The excretion of oestrogens, pregnanediol, and gonadotrophins during the normal menstrual cycle has been investigated and reviewed (Brown, Klopper, and Loraine, 1958). With the development of methods for estimating 5β-pregnane-3α,17α,20α-triol in urine, it was of interest to determine whether the excretion of this steroid varied during the menstrual cycle and whether any variations were related to the excretion of other steroids.

Materials and Methods.—The subjects were six normal females. Each subject collected urine daily from the last day of one menstruation until the first day of the next. Pregnanetriol was estimated as described by Fotherby and Love (1960) and pregnanediol by the method of Klopper, Michie, and Brown (1955).

Results

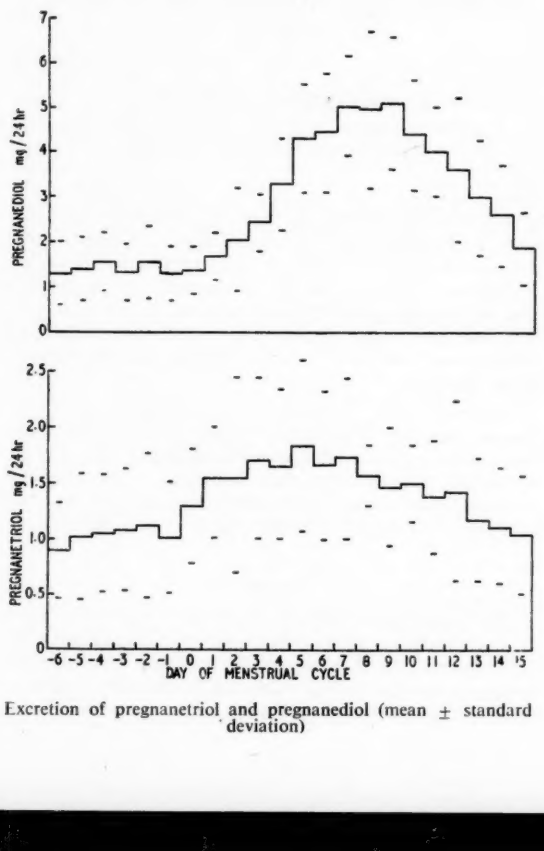
The results are shown in the Table. For comparison of the menstrual cycles, which varied in length between the subjects, the day on which the peak excretion of oestrone and oestradiol occurred during the follicular phases was referred to as Day 0. The mean values and

Excretion of Pregnanetriol and Pregnanediol (mg./24 hours) in Six Subjects

Day of Menstrual Cycle	Case A (24 Yrs)		Case B (25 Yrs)		Case C (40 Yrs)		Case D (27 Yrs)		Case E (28 Yrs)		Case F (19 Yrs)		Pregnanetriol Mean±S.D.	Pregnanediol Mean±S.D.
	Pregnanetriol	Pregnanediol	Pregnanetriol	Pregnanediol	Pregnanetriol	Pregnanediol	Pregnanetriol	Pregnanediol	Pregnanetriol	Pregnanediol	Pregnanetriol	Pregnanediol		
−8			0·5	0·5					0·75	1·0				
−7			0·5	0·5			1·7	3·8	0·75	1·4	1·6	2·4		
−6			0·4	0·6	0·5	0·9	1·5	2·7	0·8	0·9	1·3	1·4	0·90±0·43	1·30±0·74
−5			0·5	0·7	0·5	1·0	1·3	2·8	0·8	1·3	2·0	1·3	1·02±0·57	1·42±0·72
−4			0·5	0·9	0·6	0·9	1·6	2·6	0·85	1·4	1·7	1·9	1·05±0·53	1·54±0·65
−3	1·1	0·8	0·6	0·7	0·5	1·1	2·1	2·6	0·8	1·4	1·4	1·4	1·08±0·55	1·33±0·63
−2	1·1	0·8	0·6	0·6	0·7	1·1	2·5	3·0	0·65	1·8	1·2	2·0	1·12±0·65	1·55±0·82
−1	0·7	0·6	0·6	0·9	0·6	1·2	2·0	2·6	0·85	1·2	1·3	1·3	1·01±0·50	1·30±0·63
0	1·5	1·1	1·0	0·9	0·9	1·2	2·2	2·4	0·85	1·2	—	—	1·29±0·51	1·36±0·53
1	1·6	1·4	1·0	1·1	1·6	1·2	2·2	2·7	1·0	1·8	2·0	1·8	1·57±0·44	1·67±0·53
2	1·5	1·2	1·1	1·4	0·8	1·5	3·4	4·6	0·9	2·1	1·7	1·5	1·57±0·87	2·05±1·17
3	1·3	1·5	1·1	2·4	1·5	2·0	3·1	3·6	1·0	2·5	2·2	2·6	1·70±0·73	2·43±0·64
4	1·7	2·1	1·2	3·9	1·3	3·0	3·1	5·3	1·0	3·0	1·6	2·5	1·65±0·69	3·30±1·05
5	1·9	3·5	1·3	5·5	1·4	3·8	3·4	6·2	1·1	4·0	1·9	2·7	1·83±0·76	4·28±1·20
6	—	—	1·0	5·9	1·3	4·0	2·8	5·5	1·2	4·7	2·0	2·1	1·66±0·66	4·44±1·34
7	2·2	3·5	1·0	5·9	1·4	4·4	3·0	6·8	1·0	5·5	1·8	4·0	1·73±0·71	5·02±1·14
8	2·1	2·3	1·5	7·5	1·3	3·7	1·6	6·4	1·3	5·6	1·6	4·1	1·57±0·27	4·93±1·75
9	2·3	3·3	1·1	5·9	0·8	4·2	1·8	7·4	1·0	6·0	1·8	3·6	1·47±0·53	5·07±1·47
10	1·6	2·6	1·2	4·9	1·4	3·5	1·4	6·5	1·2	4·7	2·2	4·1	1·50±0·34	4·38±1·22
11	1·3	2·6	0·8	4·7	1·8	3·8	2·0	5·8	0·7	3·5	1·7	3·6	1·38±0·50	4·0 ±1·01
12	1·4	2·8	0·7	3·1	0·7	2·8	3·1	7·0	1·2	3·8	1·5	1·9	1·43±0·81	3·57±1·63
13	1·2	2·2	0·7	2·2	0·7	2·6	2·2	5·8	0·7	3·0	1·5	2·1	1·7 ±0·35	2·98±1·30
14	1·6	2·5	0·6	1·2	0·7	2·2	1·9	4·6	0·75	2·4			1·11±0·53	2·58±1·11
15	1·2	1·7	0·5	1·2	0·7	1·1	2·0	3·4	0·8	1·9			1·04±0·53	1·86±0·82
16							2·0	3·0						
17							2·1	3·0						

standard deviations for the excretion of pregnanetriol and pregnanediol are shown in the Figure.

From the beginning of the cycle until Day 0 the daily excretion of both pregnanetriol and pregnanediol was fairly constant. From Day 0 onwards the excretion of pregnanetriol began to increase; by Day 3 it had reached a value almost twice the follicular phase level, and remained at this elevated level until Day 7, when it began to decrease. The pattern of pregnanetriol excretion was different from that of pregnanediol excretion, which started to rise on Day 1 and reached a maximum value between Days 7 and 9. Thus the excretion of pregnanetriol reached a maximum value two to four days before that of pregnanediol and began to decrease two days before that of pregnanediol.



Excretion of pregnanetriol and pregnanediol (mean ± standard deviation)

Estimations of 17-ketosteroids, 17-hydroxycorticosteroids, and dehydro*epi*androsterone in urine from subjects C, D, and F showed that the excretion of these steroids did not vary during the menstrual cycle.

Discussion

It has been suggested by Solomon, Vande Wiele, and Lieberman (1956) that 17α-hydroxyprogesterone, the main precursor of urinary pregnanetriol, is an intermediate in the conversion of cholesterol to oestrogens, and Zander (1958) has identified 17α-hydroxyprogesterone in extracts of human ovaries. The pattern of pregnanetriol excretion during the menstrual cycle would probably suggest that 17α-hydroxyprogesterone has a function other than that of being an intermediate in oestrogen biosynthesis. It is of interest that esters of 17α-hydroxyprogesterone are active progestationally (Junkmann, 1957).

Pickett, Kyriakides, Stern, and Sommerville (1959), who studied only one normal subject and one adrenalectomized subject, have reported that pregnanetriol excretion varied during the menstrual cycle, but, contrary to the present results, found that in their normal subject the pregnanetriol excretion closely followed that of pregnanediol.

I am grateful to Dr. J. B. Brown for the oestrogen estimations and to Miss N. Balloch, Miss A. Fleming, and Mr. D. N. Love for technical assistance.

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PETROL-VAPOUR POISONING

BY

R. W. AINSWORTH, M.B., B.Chir.

From the Department of Pathology, University of Cambridge

Accidental death due to inhalation of petrol vapour is surprisingly rare in Britain (Aldin, 1958). Nevertheless, it is important to consider the possibility of petrol poisoning whenever illness or death occurs in patients who have been exposed to petrol. The following accident illustrates the danger of spilling petrol inside a small enclosed space.

Case Report

A boy aged 3 years 10 months was trapped in an overturned saloon car. He was discovered 5–10 minutes after the accident lying head downwards, unconscious, with his head in a pool of petrol. He died two minutes after his release without regaining consciousness. The petrol had leaked into the roof of the car from the damaged tank in the boot.

Necropsy (40 hours after death).—The body was pale and cyanosed. There were extensive areas over the trunk and limbs, where the superficial epidermis was loose and could be stripped off with ease. The bases of these excoriated areas were pale and the appearances were very similar to those seen in macerated stillbirths. In addition, there were scattered abrasions and a bruise in the left parietal region of the scalp. The heart and great vessels contained dark fluid blood. There were no petechial haemorrhages in the pericardium, pleura, or thymus. The lungs showed evidence of congestion, oedema, and intrapulmonary haemorrhage, especially in their dorsal portions. The tracheal and bronchial mucosa was hyperaemic and the bronchi were filled with haemorrhagic fluid. There was conspicuous congestion of the remaining organs, but no other significant abnormality, apart from some oedema of the brain and a strong smell of petrol, which was most obvious in the lungs.

Histological Examination.—Hyperaemia was conspicuous in all the organs examined. In addition the lungs showed considerable oedema and some intra-alveolar haemorrhage and necrosis of alveolar walls. There were occasional petechial haemorrhages in sections of brain. Slight fatty change was present in the parenchymal cells of the liver, especially in the periphery of the lobules, and the Kupffer cells throughout the liver were loaded with sudanophil material. In a section of skin from an excoriated area there was loss of much of the superficial part of the epidermis; in places it remained attached, forming intra-epidermal bullae. There was no evidence of any vital reaction in the underlying dermis.

The presence of petrol in the lungs was confirmed by simple distillation, 195 g. of lung tissue yielding 1 ml. of a fluid resembling petrol. Similar treatment of stomach contents (15 ml.), liver (200 g.), and brain (200 g.) failed to demonstrate a measurable quantity of fluid petrol.

Discussion

Death due to inhalation of petrol fumes is a recognized industrial hazard and is usually due to entering a tank or wagon containing petrol (Browning, 1953). Death due to accidental or suicidal ingestion of petrol is more common.

Petrol, or gasoline, is a petroleum distillate consisting essentially of saturated and unsaturated aliphatic hydrocarbons, but, depending on its source, it may contain varying amounts of cyclic and aromatic hydrocarbons. Aromatic hydrocarbons tend to be more toxic than paraffins, perhaps partly because they are absorbed more rapidly, while, in general, the irritant and toxic effects of a given series of like compounds increase with increase in molecular weight (Machle, 1941). The small amount of tetraethyl lead added to British petrol is unlikely to play any part in acute poisoning.

Machle (1941) states that the fatal oral dose of petrol for man is approximately 7.5 g. per kg. He does not believe that systemic poisoning can be produced by cutaneous absorption alone, though petrol can be absorbed through the skin. Poisoning by inhalation is much more rapid than by ingestion. Susceptible people may show symptoms after exposure to concentrations as low as 300 to 500 parts per million. The exact amount which will cause death in man in a short time is not known, but amounts in excess of 10,000 parts per million are rapidly fatal to most animals (Machle, 1941). A few minutes' exposure to a high concentration causes coma and death without any respiratory struggle or post-mortem signs of anoxia. Lower concentrations may cause flushing of the face, ataxia, mental confusion, slurred speech, and difficulty in swallowing—a picture similar to that of alcoholic intoxication. Delirium, coma, and tonic and clonic convulsions may occur. The blood-pressure is low and the pulse weak and rapid. Respiration is rapid and shallow. Sudden respiratory and cardiac arrest may occur (von Oettingen, 1958).

The pathological changes produced by petrol are dependant on its irritant action and its lipolytic activity. The lungs show the most constant changes: hyperaemia, petechial haemorrhages, and sometimes gross pulmonary haemorrhages and necrosis of alveolar walls. There may be subserous haemorrhages in the liver, kidney, and spleen, and haemorrhages into the serous cavities (in animals). The liver may show cloudy swelling and fatty changes, and the kidneys oedema and damage to the proximal tubules and glomeruli. Oedema and hyperaemia of the brain is usual, and extravasations of blood may occur. If death occurs within a few hours or minutes of exposure few changes may be seen other than oedema, congestion, and scattered haemorrhages in the lungs, and oedema of the central nervous system.

The case described showed some of these features, the changes in the lungs being striking. The skin lesions are similar to those described by Aidin (1958) in a youth dying of petrol-vapour poisoning. Aidin ascribed them to the effect of petrol-soaked clothing in contact with the skin, and he believed that the process went on after death. This would seem to be the most likely explanation. In the present case the boy's clothes were soaked in petrol; they were removed at another hospital, probably an hour or so after the accident. It is obvious that petrol-soaked clothing should be removed as soon as possible to prevent cutaneous absorption and possible damage to the skin.

Petrol vapour is heavier than air and the concentration in the overturned car in the region of the boy's head must have been far in excess of 10,000 parts per million. No fluid petrol was demonstrated in the stomach, but the possibility of aspiration of some fluid petrol into the lungs cannot be excluded. Such aspiration seems unlikely in view of the absence of damage to the oral and pharyngeal mucosa.

Summary

An account is given of the post-mortem findings in a small boy killed in a road accident. These findings and the circumstances of his death indicated that the primary

cause of death was inhalation of petrol vapour. Interesting skin changes, probably due to the contact of petrol-soaked clothing with the skin after death, are described.

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Medical Memoranda

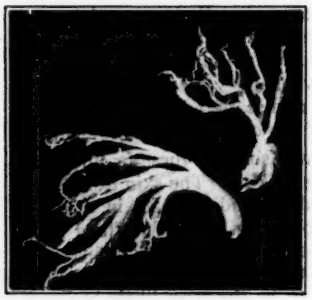
A Case of Fibrinous Bronchitis

Fibrinous or plastic bronchitis is a rare illness in which attacks of coughing and dyspnoea are associated with the presence of rough fibrinous casts in the bronchial tubes. When the patient coughs up these casts the dyspnoea is relieved. A case of this disorder is described below.

CASE REPORT

The patient, a Turkish youth aged 19, was admitted to the Sisli State Hospital on September 19, 1953, because of pronounced dyspnoea and fever. His illness had started a month previously as a chill, with fever and difficulty in breathing.

On admission he complained of intermittent pain over the praecordium, in the left shoulder, and sometimes in the abdomen, aggravated by inspiration. He was weak, dyspnoeic, had an irritative cough, and assumed a characteristic attitude of distress, sitting up and leaning forward. A friction rub, heard over the praecordium, disappeared shortly after the occurrence of a pericardial effusion. The presence of the effusion was confirmed radiologically.



Expectorated casts.

Over the next few days the pericardial fluid increased. The liver was enlarged, the jugular veins were engorged, and cyanosis of the skin and mucous membranes appeared. Heart sounds were diminished. A pericardial paracentesis was performed and a serofibrinous fluid obtained: it contained much fibrin and a few lymphocytes. A diagnosis of tuberculous pericarditis was made. The fluid was cultured and also injected into a guinea-pig. The culture remained sterile, but the guinea-pig died from tuberculous peritonitis. The patient was treated with corticotrophin. He left hospital on November 25, having recovered. About the middle of January, 1954, he again became dyspnoeic and his face cyanotic. His father noticed that during his struggles for air he obtained relief whenever he coughed up some whitish branched matter. This sputum consisted of tracheo-bronchial casts.

On examination he seemed seriously ill, being dyspnoeic and cyanotic. Chest expansion was moderately limited. Breath sounds were harsh and musical, with numerous moist rales over the base of both lungs. The size of the heart was normal, the sounds were regular, and no abnormality could be detected. No abnormalities were found in other organs. The urine was normal. Blood examination showed a slight hypochromic anaemia, and there was a slight increase in blood fibrinogen (Dr. Hatice Bodur). Clinically we accepted the case as one of "fibrinous bronchitis following mediastinal compression." *X*-ray examination (Dr. Tarik Temel) showed diffuse bronchitic changes over the entire lung area, but especially pronounced on the right side. The heart was slightly enlarged.

The white tree-like expectorated casts (see Figure) were examined microscopically (Dr. Fatih Ali Yücel) and were found to be composed of central layers of fibrin, which were oedematous, and the intervening spaces were filled with eosinophils and lymphocytes.

These findings confirmed the clinical diagnosis of fibrinous bronchitis. Aerosol treatment with hyaluronidase was begun in order to dissolve the fibrin. The last radiographs showed improvement in the bronchitic features. The size of the heart was normal.

COMMENT

No satisfactory explanation for this disorder has yet been found. Usually it follows a chronic course and may continue for years. Sometimes it is acute. The patients are mostly young adults or in early middle age, but children may also be affected. The disorder is commoner in males than females.

It occurs chiefly in association with other diseases, especially pulmonary tuberculosis or bronchial asthma, and occasionally during the course of certain acute infections. Nevertheless it may occur as a primary affection with an acute onset in an apparently healthy person. In the chronic form the disorder has a remittent course, with acute or subacute attacks at intervals.

Usually only the signs of ordinary dry bronchitis can be found on examination, but emphysematous changes in the lungs may also occur. The sputum contains tough, whitish masses, varying in size from 1 to 3 cm. in length and about 1 mm. thick, though occasionally they may be larger. They are arranged in concentric layers of material, not very solid and containing air. They consist chiefly of fibrin and mucin and contain eosinophils and neutrophils and occasionally bacteria. In some cases Charcot–Leyden crystals and Curschmann spirals are also found, suggesting a relationship with asthma.

There is a resemblance between the above case and that described by Mulligan and Spencer (1924). Their patient suffered from bronchial asthma, the symptoms of which immediately disappeared after expectoration of fibrinous casts. The cause of the disorder in that case was an enlarged thymus. After *x*-ray treatment the thymus diminished in size and expectoration of casts ceased. In our case the most probable cause seems to have been mediastinal compression by the pericardial effusion.

KEMAL SARACOGLU, M.D.,
Physician, Haydarpara State Hospital, Istanbul, Turkey.

REFERENCE

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Two new standards for sterilizers—B.S. 3219:1960: "Hospital sterilizers: horizontal cylindrical pressure steam type," and B.S. 3220:1960: "Hospital sterilizers: horizontal rectangular pressure steam type"—are now available from the Sales Branch, British Standards Institution, 2, Park Street, London, W.1, price 6s. each (postage extra to non-subscribers).

Reviews

MICROBIOLOGY

Recent Progress in Microbiology. Symposia held at the Seventh International Congress for Microbiology, Stockholm, 1958. Edited by G. Tunevall. (Pp. 453; illustrated. 70s.) Oxford: Blackwell Scientific Publications. 1959.

Here are published the six symposia held at the Seventh International Congress for Microbiology in Stockholm in August, 1958, together with an addendum on the structure and function of I.A.M.S., the International Association of Microbiological Societies. The subjects of the symposia were chosen two years before the meeting. Besides providing a survey of recent knowledge on each, the subjects survey modern microbiology. This subject, like the symposia, consists of a number of apparently unrelated methods of study directed to one scientific goal, the very principle of organic life and activity. That many of the organisms most useful for research happen to be micro-organisms (bacteria, viruses, yeast, moulds) is responsible for the belief, of some people, that microbiology is concerned only with the biology of microbes, or is a more respectable name for bacteriology. That the organizers of these symposia do not share these misapprehensions is shown by their choice of subjects, one of which concerns research on germ-free animals!

"Recombination mechanisms in bacteria" includes a brilliant discussion by Jacob and Wollman of the relation between prophage and bacterial chromosome in lysogenic bacteria. Stocker reviews transduction and Cavalli-Sforza discusses developments in bacterial recombination since 1953. Harriett Ephrussi-Taylor's masterly analysis of transformation by deoxyribonucleic acid demonstrates the essential similarity of the mechanism of incorporation to natural mechanisms of incorporation by recombination. Braun points out the weakness of bacterial classification which has borrowed the taxonomic nomenclature of higher organisms, but not its genetic basis. Bacterial genetics is indeed advancing fast and more account of it should be taken in medicine.

The fourth symposium, on latent and masked virus infections (or "viral infections" as Lwoff states to be etymologically correct), can be regarded as a wider treatment of the subject analysed genetically in the paper on lysogenic bacteria. It is significant that Burnet, in his résumé, considers the genetical approach as likely to be the most fruitful, and thinks that the best way of regarding the virus-cell relationship is as the intrusion of one genetic system into the domain of another.

The discussion of the roles of nucleic acid in protein synthesis and of protein in nucleic acid synthesis provides a satisfying summary of these intricate relationships. It includes Ochoa's account of the biosynthesis of ribonucleic acid and a short reference to Kornberg's enzyme, which catalyses the synthesis of deoxyribonucleic acid. The third symposium, on tissue-specific antibodies, like the fifth one on germ-free animals, shows that the conference was not merely concerned with the biology of microbes. Two of the contributions deal particularly with techniques, the others with auto-antigenicity and with tolerance and auto-immunity.

Reyniers describes the installations, developed first in the Lobund Laboratories at the University of Notre Dame (Indiana), needed to produce germ-free animals and to use them for research. Obviously this type of work is expensive in every respect. The ways in which symbiosis with microbes (not merely commensalism) influences animals in their growth, development, metabolism, and immunology are of great interest. The effects are sometimes bizarre, like the enlarged caecum of rats. The final symposium was on continuous culture methods. These have important scientific applications and potential value in industry, dependent upon the solution of technical problems.

D. G. CATCHESIDE.

INBORN ERRORS OF METABOLISM

Inborn Errors of Metabolism. By David Yi-Yung Hsia, M.D. (Pp. 358; illustrated. 72s.) Chicago: Year Book Publishers. London: Interscience Publishers Ltd. 1959.

In no medical field has the impact of modern biochemical techniques been more apparent than in the study of the inborn errors of metabolism. The detailed analysis of many of these conditions has resulted in a mass of information which is confusing, not only to students but to all who are concerned with these problems. The activity in this field and potential for further rapid development were clearly indicated at the recent Congress of Paediatrics in Montreal. It is therefore timely that Dr. Hsia should have published a book covering this field which is a model of concise presentation.

The book begins with a lucid exposition of the main principles underlying the concept of an "inborn error of metabolism" and the criteria upon which the existence of such a fault should be based. Each of the main conditions, now classified as an inborn metabolic fault, is then systematically discussed. In each case the essential information on clinical features, heredity, pathogenesis, diagnosis, and treatment are given, and a useful bibliography is provided. A series of charts have been prepared which illustrate by means of a sample family tree the main genetic features, and indicate the primary gene effect and resultant clinical signs and symptoms. Some indication of likely future developments is also provided, and a useful appendix giving details of the main diagnostic investigations is included. This book should be of great value to all students of medicine or medical biochemistry; it should also find a place on the bookshelf of all doctors who wish to keep abreast of these developments in medicine or need factual information on this important subject.

A. C. FRAZER.

GENETICS MINUS DROSOPHILA

An Introduction to Medical Genetics. By J. A. Fraser Roberts, M.A., M.D., D.Sc., F.R.C.P. Second edition. (Pp. 263+x; illustrated. 35s.) London: Oxford University Press. 1959.

The first edition of this book published in 1940 found ready acceptance, for it dealt with genetics in medical terms instead of presenting it in a mixture of animal and plant lore laced with genetic history beginning with Mendel. Furthermore, it took special care to avoid mentioning drosophila—that bugbear of medical readers. As a result this book did more than any other text in recent years to stimulate interest in medical genetics. A second edition has been long overdue, and its appearance is therefore all the more welcome.

Simple as the first edition was, the present volume—very largely rewritten—is even simpler, for much that was still in a formative stage twenty years ago is now either discarded or more fully developed, and so more readily understandable. The discussion on partial sex-linkage is very much shortened, while the complexity of multiple alleles has become reduced as a result of the substantial work on blood groups in recent years. Genetic linkage, too, is simpler, and a more balanced view can now be taken of the gene as part of an integrated system of genes. The present volume contains two particularly useful concluding chapters, one on variation and multifactorial inheritance and their bearing on common diseases, and the other on genetic prognosis. An addendum discusses the exciting new work on chromosome abnormalities in relation to disease, and here Dr. Roberts has fallen from grace by bringing in drosophila. He should, however, have no difficulty in correcting this lapse in the inevitable third edition, which it is to be hoped will come well before another twenty years.

ARNOLD SORSBY.

THE TRIAL OF AUGUST SANGRET

The Trial of August Sangret. Edited by Macdonald Critchley, M.D. (Pp. 235+xxxiv. 18s.) London, Edinburgh, Glasgow: William Hodge and Co., Ltd. 1959.

The Trial of August Sangret will prove a fascinating and thought-provoking book to a large public. The detective-story enthusiast will enjoy the building up of circumstantial evidence, the sociologist the analysis of the characters of the two main figures in the drama, and the lawyer the fine description of a lengthy and somewhat complicated trial; the doctor, and in particular the forensic pathologist, will be left wondering. Indeed, anyone who reads this book with intelligence will be made to think and to realize how both law and medicine are constantly advancing.

In this day and age of capital and non-capital homicide, Sangret would hardly have been executed for murdering his girl friend, however viciously, upon the evidence given in this book, particularly as the jury made a strong recommendation to mercy. Indeed, in the light of recent events one wonders whether a French Canadian of Indian descent who could neither read nor write might not have had his "fitness to plead" put to the jury to some purpose. This illiteracy must have made it very difficult for him to check his own statement to the police or to instruct counsel for the defence.

In his analysis of the victim, Joan Wolfe, Dr. Critchley points out the extraordinary association of "religiosity," as he terms it, and sensuality, which is perhaps not as rare as many think. His discussion of the underlying characters of wall-writers is also fascinating. In her *graffiti* Joan Wolfe combined sentimental and religious themes—an association which is certainly more understandable. In the accused, August Sangret, the author sees a handsome, powerful, libidinous soldier, thousands of miles from home and social responsibility, if he ever had any. This description must fit a rather large proportion of military personnel serving abroad in time of war. The attraction of teenagers for much older American servicemen, and vice versa, strikes Dr. Critchley as peculiar, but surely it is simply and materially understandable.

From the point of view of the pathological evidence there arise several points for discussion, even though the case is now inevitably concluded. There is the extraordinary advanced state of decomposition at which the body had arrived between September 13 and October 8; this clearly puzzled the pathologists at the time and must leave some of us thinking to-day. Indeed, Dr. Gardner in his evidence states that on October 8 "the body had been there for more than a month" (Joan Wolfe was seen alive on September 13). This may be an error in the reproduction of a note taken at the time, for it does not appear to have been seized upon by the defence. Another controversial point relates to the causation of three injuries to the skull described as stab wounds and said to be consistent with having been inflicted with a Service knife which is traced somewhat deviously into Sangret's possible possession. A photograph of one of these "stab wounds" is reproduced in the book, and one can only say that if it was not caused by the exit of a bullet then it could be certainly used for teaching purposes as an illustration of that type of wound. It does seem possible from the description of the skull as being "in a large number of broken pieces" when the soil was removed that bullet entrance wounds could have been missed.

Perhaps after all it was "capital homicide" and in fact August Sangret would have been executed even in this day and age.

DONALD TEARE.

TRADITIONAL TUTORIAL WISDOM

How to Learn Medicine. By A. E. Clark-Kennedy, M.A., M.D., F.R.C.P. (Pp. 227. 12s. 6d.) London: Faber and Faber. 1959.

In recent years a number of medical schools have adopted the tutorial system of teaching. Under this system the student spends an hour with his tutor once a week or a fortnight, either alone or with not more than two other students. There is commonly a break between preclinical and clinical studies, but within these two subdivisions it is probably best to rely on one tutor to take the student the whole way through. This is because tutorials should not be periods for quizzes or coaching, except with the failed student, for whom such departures are permissible, but rather periods for helping the student in the art of learning and in solving the emotional problems and doubts which hard study and contact with sickness and death may induce.

Clark-Kennedy's book performs just such a function. It covers the transition from school to university, and the preclinical and the clinical subjects. Much of it deals with things which should be common knowledge, such as methods of reading and note-taking and practice in *viva voce* examinations and writing papers; but it is surprising how ignorant many students are of these matters. Dr. Clark-Kennedy is a great believer in the student's keeping his own notebook, which will eventually become his system of medicine. My own belief is that taking notes is valuable because a second reading of them, not more than a day or two later, stamps the impress of the lecture on the mind, but an accumulation of notes can become an incubus.

Dr. Clark-Kennedy gives us what might be called the traditional tutorial wisdom. He does not venture deeper into the learning process, and, indeed, the recent conference of the Association for the Study of Medical Education on methods of learning and techniques of teaching shows how little is known about that. In a world into which fifty million children are born each year we ought to have better guides to education than the speculations of Plato and Dewey. There is much to

suggest that most of us use only a fraction of our potential brain-power, and this may well be one of the most profitable fields of research for mankind in the future.

L. J. WITTS.

ALL ABOUT INJURIES

Trauma. By Harrison L. McLaughlin, M.D. (Pp. 784+xiii; illustrated. £6 6s.) Philadelphia, London: W. B. Saunders Company. 1959.

Trauma "cuts across all branches of medicine with a superb disdain for the man-made boundaries of the different specialties." The writing of a book on such a wide subject is not an easy task. Professor McLaughlin and his colleagues of the Colombia-Presbyterian Medical Centre in New York have presented in a clear and well-balanced manner the many aspects of injuries to all parts of the body. The book is easy to read and an outstanding contribution to this wide and increasingly important subject.

The first part covers the local and general responses to injury and the principles governing their management. It emphasizes the importance of avoiding all delays in starting treatment. In successive chapters injuries to all parts of the body are considered by specialists in each region. Professor McLaughlin himself has written most of the chapters on injuries to the locomotor system, comprising about half of the book. He has given a great deal of thought to the forces responsible for various bone-and-joint displacements with their associated and important soft-tissue injuries, after which he advises a logical method of treatment for all torn and displaced structures. To these clear descriptions he has added most excellent line drawings. Indeed, all the illustrations of this book are well chosen and of the highest quality. Methods of treatment are often dogmatically expressed, particularly in the section on fractures. Not all experienced surgeons will agree with everything recommended. But was there ever a book on surgical treatment that gained universal agreement?

Much has yet to be learned about the detailed anatomy of many, perhaps most, injuries; only when this knowledge is gained will agreement on methods of treatment be attained. This work describes very clearly the present knowledge of its various contributors, and the treatment recommended follows logically on this basic knowledge. I shall benefit from this book and recommend it to both junior and senior surgeons responsible for the care of the injured.

WILLIAM GISSANE.

NUTRITION FOR STUDENTS

Principles of Nutrition. By Eva D. Wilson, Katherine H. Fisher, and Mary E. Fuqua. (Pp. 483+xii; illustrated. 48s.) New York: John Wiley and Sons, Inc. London: Chapman and Hall, Ltd. 1959.

This book is a well-documented and illustrated textbook on nutrition. Though it is elementary in treatment, it does, nevertheless, provide some detail, but the reviewer doubts if doctors in this country will readily react in a positive way to the opening pages, which are more attuned to a lecture to nurses and junior dietetians. This is a pity, for there is some quite good stuff in the book. The amusing little diagrams which take the place of chemistry may or may not be appreciated by the reader. It is not for the senior medical library but will find a useful place in student libraries.

D. P. CUTHBERTSON.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Atlas der Gynäkologischen Operationen. By Professor Dr. O. Käser and Dr. F. A. Iklé. (Pp. 451+viii; illustrated. DM. 148.) Stuttgart: Georg Thieme Verlag. 1960.

Les Manipulations Vétebrales. By Robert Maigne. Preface by Professor de Sèze. (Pp. 246; illustrated. NF. 28.) Paris: Expansion Scientifique Francaise. 1960.

Prophylaxie et Traitement des Escarres de Décubitus. By R. Vilain. Preface by Dr. R. Gueullette. (Pp. 120; illustrated. NF. 50.) Paris: Expansion Scientifique Francaise. 1960.

Biographical Memoirs of Fellows of the Royal Society. 1959. Volume 5. (Pp. 279; illustrated. 30s.) London: The Royal Society. 1960.

Atti della Società Italiana di Cardiologia. Twenty-first Congress, Rome, May 28-30, 1959. Volume II, *Comunicazioni.* (Pp. 598; illustrated.) Rome: Editi a Cura della Segreteria della Società. 1959.

Das Asthma Bronchiale und Seine Behandlung: Hormontherapie, Spezifische Desensibilisierung, Höhenkuren. By Professor Dr. Gottfried Holler. (Pp. 247+vi; illustrated. 94s.) Vienna, Bonn, Berne: Wilhelm Moudrich. 1960.

Documenta Geigy. Scientific Tables. Fifth edition (with Supplement). (Pp. 547. 96s.) Basle, New York: S. Karger. London: Interscience Publishers, Ltd. 1959.

The British and Overseas Pharmacist's Year Book, 1960. (Pp. 112+xvii. 5s.) London: British and Colonial Druggist, Ltd. 1960.

High Blood Pressure and Pregnancy. By Lance Townsend, M.D., B.S., F.R.C.S.(Edin.), F.R.A.C.S., F.R.C.O.G., D.T.M.&H. (Pp. 115+viii; illustrated. 40s.) Melbourne: Melbourne University Press. London: Cambridge University Press. 1959.

Handbook of Aging and the Individual: Psychological and Biological Aspects. Edited by James E. Birren. (Pp. 939+xii; illustrated. £5.) Chicago: University of Chicago Press. London: Cambridge University Press. 1959.

Efficiency Methods in the Hospital. Proceedings of the Eleventh International Hospital Congress held in Edinburgh, June 1-6, 1959. Under the Patronage of the Secretary of State for Scotland. (Pp. 207. 20s. to Members of the I.H.F., 25s. to Non-members.) London: International Hospital Federation. 1960.

Essentials of Fluid Balance. By D. A. K. Black, M.D., F.R.C.P. Second edition. (Pp. 135+xii. 20s.) Oxford: Blackwell Scientific Publications. 1960.

Recent Research in Freezing and Drying. Edited by A. S. Parkes, C.B.E., F.R.S., and Audrey U. Smith, D.Sc., M.B., B.S. (Pp. 320+vii; illustrated. 63s.) Oxford: Blackwell Scientific Publications. 1960.

The Future of Man. The B.B.C. Reith Lectures, 1959. By P. B. Medawar, F.R.S. (Pp. 128. 10s. 6d.) London: Methuen and Co., Ltd. 1960.

An Introduction to Electronics for Physiological Workers. By I. C. Whitfield, D.Sc. Second edition. (Pp. 263+xi; illustrated. 18s.) London: Macmillan and Co., Ltd. 1959.

Clinical Physiology. Edited by E. J. Moran Campbell, B.Sc., Ph.D., M.D., M.R.C.P., and C. J. Dickinson, B.A., B.Sc., B.M., M.R.C.P. Foreword by Sir Robert Platt, Bt., M.D., M.Sc., LL.D., F.R.C.P. (Pp. 530+xi; illustrated. 50s.) Oxford: Blackwell Scientific Publications. 1960.

The Avian Embryo: Structural and Functional Development. By Alexis L. Romanoff. (Pp. 1,305+xvi; illustrated. £10 10s.) New York and London: The Macmillan Company, New York. 1960.

A Guide to the Identification of the Genera of Bacteria with Methods and Digests of Generic Characteristics. Based on Data Given in the Seventh Edition of Bergey's Manual of Determinative Bacteriology and on Original Papers. By V. B. D. Skerman. (Pp. 217+ix. 44s.) Baltimore, Maryland: Williams and Wilkins Company. London: Baillière, Tindall and Cox, Ltd. 1960.

Bentley and Driver's Textbook of Pharmaceutical Chemistry. By J. E. Driver. Seventh edition. (Pp. 728+ix; illustrated. 63s.) London, New York, Toronto: Oxford University Press. 1960.

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REMISSIONS IN DIABETES

Diabetes mellitus, once diagnosed, is usually a life-long disease which calls for constant control, so that the rare cases where the disease recedes completely warrant full study. Firstly, there are those rare examples of "complicated" diabetes mellitus in which this is merely part of another endocrine syndrome. Diabetes is found in 25% of cases of acromegaly,[1 2] in 25% of cases in Cushing's syndrome,[3 4] and in perhaps 10% of cases of phaeochromocytomata.[5 6] Here detection and removal of the primary disease, which is characterized by overproduction of insulin antagonists, are usually followed by the remission of the diabetes mellitus, though not always, particularly in the acromegalic cases. On the same basis we can understand how the supervention of adrenocortical deficiency[7] or of anterior pituitary deficiency[8 9] would considerably ameliorate the diabetes mellitus and may even lead to its complete remission. Although, especially during hyperglycaemic or ketotic attacks, diabetes mellitus is apt to lead to pituitary necrosis,[10] such a complication probably explains only a few of the unexpected remissions.

When the diabetes has not been dependent on another syndrome but is mild, a remission may also occur on the removal of some important precipitating factor. For instance, the diabetes may have been discovered when an infection was being treated and recede with its cure, or may recede when excessive weight is lost by dieting.[11] However, more usually even after removal of such precipitating causes the diabetes still requires control.

While the diagnosis of diabetes mellitus implies lack of effective action by insulin, this may be due to excess of antagonists in conjunction with an insufficient insulin reserve, a situation which is potentially reversible. An illustration of it is seen in the hereditary obese hyperglycaemic mice, whose hyperglycaemia does not respond to tolbutamide, though at necropsy the pancreatic islets are found to be hypertrophied.[12] In mild diabetes mellitus L. L. Madison and R. H. Unger[13] have found that the fall in blood sugar after an intravenous test dose of tolbutamide is subnormal, this indicating a reduced but not absent insulin reserve. This agrees with the finding of G. A. Wrenshall and colleagues[14] that the pancreas of obese adult-type diabetics, but not of the juvenile-type, contains extractable insulin, though in subnormal amounts. Hence, if cure of infection or reduction of obesity improves a subject's sensitivity to insulin, the amount he secretes may again be adequate for the normal control of his blood sugar. However, his insulin reserve is likely still to be low, and to be inadequate should the stress again return. But even when there has been no evidence of any such precipitating factor, and the diabetes has been severe, complete remission has occurred at times apparently spontaneously. In thin young subjects a diabetic syndrome of sudden onset and severe enough to cause obvious ketosis, and even ketotic coma, may remit after some months so completely that a glucose-tolerance test gives a normal result on an ordinary diet and without insulin.[15–20] While such cases suggest that some precipitating agent was temporarily at work, none has been detected, though recent excessive sugar consumption was suggested for one subject.[19]

The recent studies on "prediabetes" suggest that all these cases of remission are in subjects with latent diabetes, probably both before and after the temporary episode of mild or severe diabetes mellitus. The disease is therefore more than normally liable to a recrudescence. It is perhaps rather astonishing that prediabetes, with its liability to complicate pregnancy and to entail the birth of large babies, may precede manifest diabetes by decades; clearly our blood-sugar tests are not the most sensitive index of this disease in its early stages. Conn's new cortisone-load test can bring out hyperglycaemia in a wide range of such subjects—in many relatives of diabetics, in many obese subjects, and in many mothers of large babies—and by it the physician can forecast the later development of diabetes mellitus.[16] This test is thought to be a measure of the patient's insulin reserve. L. J. Stutman and colleagues[20] found that a

[1] Coggeshall, C., and Root, H. F., *Endocrinology*, 1940, **26**, 1.
[2] Natelson, R. P., *Ann. intern. Med.*, 1954, **40**, 788.
[3] Plotz, C. M., Knowlton, A. I., and Ragan, C., *Amer. J. Med.*, 1952, **13**, 597.
[4] Sprague, R. G., *Proc. roy. Soc. Med.*, 1953, **46**, 1070.
[5] de Vries, A., Rachmilewitz, M., and Schumert, M., *Amer. J. Med.*, 1949, **6**, 51.
[6] Goldner, M. G., *J. clin. Endocr.*, 1947, **7**, 716.
[7] Stanton, E. R., Jones, H. W., and Marble, A., *A.M.A. Arch. intern. Med.*, 1954, **93**, 911.
[8] Mathisen, H. S., *Acta med. Scand.*, 1953, **145**, 326.
[9] Grunberg, A., and Blair, J. L., *Brit. med. J.*, 1957, **2**, 439.
[10] Brennan, C. F., Malone, R. G. S., and Weaver, J. A., *Lancet*, 1956, **2**, 12.
[11] Newburgh, L. H., and Conn, J. W., *J. Amer. med. Ass.*, 1939, **112**, 7.
[12] Gepts, W., Christophe, J., and Mayer, J., *Diabetes*, 1960, **9**, 63.
[13] Maddison, L. L., and Unger, R. H., *J. clin. Invest.*, 1958, **37**, 627.
[14] Wrenshall, G. A., Bogoch, A., and Ritchie, R. C., *Diabetes*, 1952, **1**, 87.
[15] Harwood, R., *New Engl. J. Med.*, 1957, **257**, 257.
[16] Conn, J. W., *Diabetes*, 1958, **7**, 347.
[17] Peck, F. B., Jr., Kirtley, W. R., and Peck, F. B., Sr., ibid., 1958, **7**, 93.
[18] Cheng, T. O., Jahraus, R. C., and Traut, E. F., *J. Amer. med. Ass.*, 1953, **152**, 1531.
[19] del Greco, F., and Scapellato, L., *Diabetes*, 1953, **2**, 457.
[20] Stutman, L. J., and Hayes, J. D., ibid., 1959, **8**, 189.

severe diabetic in remission was still abnormal on Conn's test, and was therefore a prediabetic whose insulin reserve was probably subnormal.

COMPLICATIONS OF INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis is of particular interest to the clinician because of the diversity of diseases simulated. The lymphoid and reticulo-endothelial hyperplasia characteristic of its pathology, though apparent clinically only in the lymph nodes and perhaps the tonsils in most cases, may be present in almost every organ of the body, and when severe may produce puzzling focal manifestations which often obscure the underlying nature of the disease. A striking example is spontaneous or traumatic rupture of the spleen, which may occur in an enlarged, softened spleen with its architecture disrupted and its capsule stretched owing to gross infiltration with lymphocytes and monocytes. This was the cause of death in 8 of a series of 21 fatal cases.[1] A similar type of infiltration in the periportal and sinusoid areas of the liver is revealed by biopsy in some 85 to 100% of cases.[2] The hepatic lesion is indistinguishable in most instances from that of acute infectious hepatitis, but overt jaundice is present only in some 5%.[3] Abdominal pain simulating appendicitis may be caused by hyperplasia of lymph nodes in the region palpated at McBurney's point,[4] and in the upper abdomen by infiltration of the pancreas.[5]

J. D. Bergin,[6] in New Zealand, has recently reviewed the literature on neurological complications, and added a case of his own. W. Erwin and colleagues,[2] in Kansas City, U.S.A., have also recently described five cases illustrating neurological and haematological complications. The complications included encephalitis (fatal), peripheral neuropathy with permanent winged scapula, transverse myelitis, and haemolytic anaemia. The incidence of neurological complications is about 1–2%,[6] but the case-fatality rate may reach 15 to 40%. Signs may develop of meningitis, encephalitis, peripheral neuritis, ataxia, nystagmus, hyperaesthesia, mental confusion, or coma. Over 20 cases have been reported of the Guillain–Barré syndrome, characterized by bilateral symmetrical ascending paralysis and cell-protein dissociation in the spinal fluid. In 1954 O. R. Tanner[7] reviewed the ocular complications—conjunctivitis, oedema of eyelids, uveitis, optic neuritis, papilloedema, and retinal haemorrhage—probably all associated with local lymphocytic and monocytic infiltrations. Radiographic evidence of pulmonary complications has been found in 2.7%—mainly interstitial pneumonitis and virus pneumonia.[8 9] Similar infiltrations have been detected in the renal cortex and in the myocardium[8]; and clinical and electrocardiographical evidence of pericarditis has been adduced in several recent reviews.[10 11]

Acute haemolytic anaemia, first described in 1943,[12–14] and acute thrombocytopenic purpura, which has been increasingly recognized in the past 10 years,[15–17] are of special interest in view of their possible allergic origin. There is little evidence of infiltration of bone-marrow in these cases, and it is supposed that the lesions may be the result of destructive antigen–antibody reactions, the relevant antigens perhaps being produced by virus action on the red cells and platelets. The Coombs test may or may not be positive, and the response to treatment with cortisone or A.C.T.H., though suggestive, is often uncertain. It is important that all such cases be fully investigated and reported.

In addition to such systemic complications, rare cases occur of extreme swelling of the tonsils, adenoid tissue, and cervical lymph nodes, sometimes with production of thick membranous exudate simulating that of diphtheria. Some of these in the past have been fatal from respiratory obstruction and the toxaemia of secondary bacterial infection. Nowadays treatment with steroids combined with antibiotics is likely to relieve the angina and so save life.

FAMILIAL DISTURBANCES OF BILIRUBIN METABOLISM

In 1956 the mystery of the mechanism by which bilirubin passed from the blood through the liver into the bile was solved by the simultaneous discovery by B. H. Billing and G. H. Lathe[1] in Great Britain, R. Schmid[2] in the United States, and E. Talafant[3] in Czechoslovakia of its conjugation as a glucuronide. This process converts the van den Bergh reaction of the serum bilirubin from "indirect" to "direct," and the increased water solubility of the bilirubin glucuronide allows its excretion in the urine. This advance has led to increased interest in familial disturbances of bilirubin metabolism. These and

[1] Shinton, N. K., and Hawkins, C. F., *Lancet*, 1956, **2**, 708.
[2] Erwin, W., Weber, R. W., and Manning, R. T., *Amer. J. med. Sci.*, 1959, **238**, 699.
[3] Wormer, D. C., Martin, W. J., and Wollaeger, E. E., *Ann. intern. Med.*, 1956, **45**, 718.
[4] Gilbert, R. L., *Wisc. med. J.*, 1949, **48**, 925.
[5] Myhre, J., and Nesbitt, S., *J. Lab. clin. Med.*, 1949, **34**, 1671.
[6] Bergin, J. D., *J. Neurol. Neurosurg. Psychiat.*, 1960, **23**, 69.
[7] Tanner, O. R., *A.M.A. Arch. Ophthal.*, 1954, **51**, 229.
[8] Wechsler, H. F., Rosenblum, A. H., and Sills, C. T., *Ann. Intern. Med.*, 1946, **25**, 113.
[9] Custer, R. P., and Smith, E. B., *Blood*, 1948, **3**, 830.
[10] Roseman, D. M., and Barry, R. M., *Ann. intern. Med.*, 1957, **47**, 351.
[11] Webster, B. H., *Amer. J. med. Sci.*, 1957, **234**, 62.
[12] Dameshek, W., *J. Amer. med. Ass.*, 1943, **123**, 77.
[13] Hall, B. D., and Archer, F. C., *New Engl. J. Med.*, 1953, **249**, 973.
[14] Perrier, C. V., and Rousso, C., *Schweiz. med. Wschr.*, 1959, **89**, 766.
[15] Angle, R. M., and Alt, H. L., *Blood*, 1950, **5**, 449.
[16] Ogilvie, C. M., and Parry, T. E., *Brit. med. J.*, 1952, **2**, 977.
[17] Douglas, W. A. C., *Med. J. Aust.*, 1959, **2**, 564.

other causes of jaundice in infancy are discussed by Dr. A. E. Claireaux at p. 1528 this week.

The usual form of congenital non-haemolytic jaundice is the Gilbert type.[4] Mild jaundice, increased by fatigue or infections, is seen without other physical signs, with normal biochemical tests of liver function and with normal hepatic structure as seen by needle biopsy. The jaundice is due to the accumulation in the blood of unconjugated bilirubin. Although deficiency of the enzyme glucuronyl transferase, which allows the bilirubin to conjugate with glucuronide, has been thought to occur in the more severe forms of the disease, it does not seem to be so in the common, milder variety.[5] Tolerance to intravenously administered bilirubin is impaired, and it seems that the liver cells in some way lack their normal capacity for taking up bilirubin.[6]

The next variety of congenital non-haemolytic jaundice was described independently in 1954 by I. N. Dubin and F. B. Johnson[7] and by H. Sprinz and R. S. Nelson.[8] It is also familial, mild, and harmless. It differs from the Gilbert variety in three respects: the bilirubin in the serum is conjugated as well as unconjugated, the gall-bladder is not visualized by oral cholecystography, and the liver cells are packed with an unidentified black pigment probably related to the lipofuscins.[9] More recently A. B. Rotor and co-workers[10] from the Philippines, L. Schiff and others,[11] and B. J. Haverback and S. K. Wirtschafter[12] have described yet another variant resembling the Dubin–Johnson type in the increase of both types of pigment in the serum but differing in that the gall-bladder is visualized on oral cholecystography and there is no black pigment in the liver cells. In both types there is presumably not only difficulty in uptake of unconjugated bilirubin by the liver cells but also in its secretion, after conjugation, into the biliary passages.

A further interesting possibility is raised by the recent description by L. G. Israels and others[13] of four patients with jaundice occurring in two Mennonite families in Southern Manitoba. Jaundice and splenomegaly developed in early life. The bilirubin in the serum was predominantly unconjugated and the survival of red cells somewhat shortened before splenectomy. Although spherocytes were noted in the peripheral blood, osmotic fragility of red cells was normal. Excretion of urobilinogen in urine and stools was high. Haemolysis, when present, was corrected by splenectomy, but the reticulocytosis, normoblastic hyperplasia of the marrow, hyperbilirubinaemia, and increased excretion of urobilinogen persisted. The liver showed haemosiderosis. It is suggested that the excess bilirubin came from the marrow erythrocytes or their precursors—that is, from a source other than the circulating red cell—and the primary overproduction of bilirubin has been termed "shunt hyperbilirubinaemia." This suggestion is in keeping with earlier observations of I. M. London and his associates[14] that in normal subjects a small proportion of stercobilin in the faeces does not come from breakdown of mature circulating erythrocytes. The patients described by Israels and co-workers may show an exaggeration of this normal process of producing bile pigment.

These cases of familial hyperbilirubinaemia are of great theoretical interest for the better understanding of the mechanism of all forms of jaundice. Their recognition is also of practical significance, for it may prevent a jaundiced person with a harmless condition from being labelled a cirrhotic or even being exposed to an unnecessary laparotomy for diagnosis. Investigation of these patients must be thorough and should include partition of bilirubin in the serum, the bromsulphthalein tolerance test, biochemical tests of liver function, examination of the peripheral blood, cholecystography, and in some cases needle biopsy of the liver and measurement of urinary and faecal excretion of stercobilinogen. Investigation of siblings may also be of help in coming to a diagnosis.

THYROID AND ADRENAL MEDULLA

The thyroid hormones increase the sensitivity of the tissues to the effects of the hormones of the adrenal medulla, the catechol amines adrenaline and noradrenaline.[1] W. R. Brewster and his colleagues[2] concluded from experimental work that there was a dynamic interrelationship between the thyroid and adrenal medullary hormones and sympathetic nerve endings. While augmentation of the effects of adrenaline and noradrenaline by the thyroid hormones is generally accepted, there is some reluctance to agree with their contention[2] that this wholly explains the metabolic effects of the thyroid. For example, isolated hearts from thyroxine-injected animals beat at a faster rate immediately after removal than those of animals not given thyroxine.[3–5] Since such a preparation has been deprived of its sympathetic nerve

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supply and the other source of catechol amines, the adrenal medulla, these findings were advanced as evidence of the direct effect of thyroxine upon the heart. However, such experiments do not necessarily isolate the activity of the thyroid hormones from that of adrenaline and noradrenaline, since heart muscle avidly takes up and retains the catechol amines,[6] and if the isolated heart is kept beating for four hours there is little difference in heart rate after this time in thyroxine-injected and euthyroid animals.[7] Furthermore, the heart muscle of thyroxine-injected rats and sheep shows an increase in the concentration of the catechol amines.[8 9]

Both thyroxine and triiodothyronine potentiate the action of adrenaline on isolated intestinal muscle, as shown by the inhibition of peristalsis, and it is of interest that both hormones have a latent period of action.[10] On the other hand, increased peristalsis of the gut, with diarrhoea, is not infrequently associated with hyperthyroidism in man, and this, with many other features of the disease, including the peripheral vasodilatation, cannot be explained on the basis of the potentiation of the effects of the catechol amines. Moreover, this potentiating effect is not a monopoly of the thyroid hormones, since the presence of the adrenal steroids is known to be necessary for the proper action of the catechol amines.[11]

The effects of adrenaline are increased in euthyroid subjects in whom hyperthyroidism has been induced by the ingestion of triiodothyronine as well as in patients with clinical thyrotoxicosis.[12] This finding suggests that it is the concentration of circulating thyroid hormone which influences the response to the catechol amines and not some unrecognized factor in thyrotoxicosis. This interrelationship between the hormones of the thyroid and those of the adrenal medulla cannot be accounted for by the increase in basal metabolic rate produced by the thyroid, since individuals with high basal metabolic rates due to causes outside the thyroid react normally to adrenaline.[12] Furthermore, hypermetabolism produced by ingestion of salicylate is not associated with increased sensitivity to adrenaline.[13] The explanation may lie in the capacity of the thyroid hormones to diminish the rate of destruction of adrenaline and noradrenaline in the tissues.[1] They do this by inhibiting the activity of amine oxidase, since this enzyme increases the rate of destruction of the catechol amines by oxidation and deamination. This hypothesis is supported by the fact that the concentration of amine oxidase in the liver[14] and blood vessels[15] is decreased in animals injected with thyroxine.

Knowledge of the increased sensitivity to the catechol amines produced by the thyroid hormones has been applied to both the diagnosis and treatment of thyrotoxicosis. For example, because reserpine depresses sympathetic activity, probably through its hypothalamic effects, it has been used in the treatment of thyrotoxicosis,[16] though the toxic effects of the drug in the doses necessary to obtain relief of symptoms would appear to limit its use to the treatment of thyroid crisis.[17] The diagnostic application of the increased sensitivity to adrenaline found in thyrotoxic subjects was first proposed by E. Goetsch.[18] Now J. F. Murray and J. J. Kelly[12] have devised a modification of his test which they claim is safe and discriminates well between thyrotoxic and euthyroid individuals. They measured the percentage change in heart rate and pulse pressure in response to intravenous adrenaline given at an increasing rate of flow. The greater circulatory effects of adrenaline discriminated the thyrotoxic group from the euthyroid group. These authors did not make a special study of cases which had caused clinical diagnostic difficulty—i.e., mild thyrotoxicosis—though for the clear evaluation of any diagnostic test of thyroid function it is desirable to do so. Furthermore, some middle-aged or elderly patients suspected of having thyrotoxicosis have coronary artery disease with or without a cardiac arrhythmia, and for them an intravenous infusion of adrenaline would be contraindicated. The test may, however, have some application in young patients when facilities for radioactive-iodine studies and estimations of protein-bound iodine are not available.

The advent of each new test of thyroid function provides the opportunity to emphasize the importance of a therapeutic trial with an antithyroid drug as a diagnostic measure in cases presenting diagnostic difficulty.

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MEASLES VIRUS AND GIANT-CELL PNEUMONIA

Five years ago J. F. Enders and T. C. Peebles[1] discovered how to cultivate the measles virus in the laboratory. They found that when blood or pharyngeal washings, collected in the early stages of typical attacks of measles, were introduced into certain tissue cultures, the cells degenerated, with the formation of large giant cells, and that the nuclei of affected cells showed striking intranuclear inclusions. Similar inclusions and giant cells called Warthin–Finkeldey cells are found in pathological material obtained from cases of measles. This discovery opened the way for much further work—including efforts to prepare a vaccine—which would otherwise have been impossible or very difficult. All this work has been thoroughly reviewed recently by

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K. McCarthy.[2] Antigens prepared from infected tissue-cultures can be used for the detection of measles antibodies by neutralization and complement-fixation tests. Such tests have shown that antibodies to the virus appear towards the end of the illness and may be found in most persons giving a history of an attack of measles.

By applying the new laboratory techniques, Enders and his colleagues[3] have recently illuminated an obscure clinical problem—namely, that of giant-cell pneumonia. This disease affects debilitated children; and is characterized pathologically by interstitial pneumonitis and a predominantly mononuclear exudate with giant cells containing eosinophilic intranuclear and cytoplasmic inclusions. V. Hecht,[4] in 1910, was the first to describe the disorder. Others have reported cases since his publication, and it has been suggested, without any conclusive evidence, that the disease may in some cases be due to measles or canine-distemper virus—two viruses which seem to be related. Of the three typical cases described by Enders and his colleagues two had a history of contact with measles, but one had not, and none had a rash or other characteristic signs of measles. All had chronic diseases (mucoviscidosis, leukaemia, or Letterer–Siwe disease). Virus was recovered from the lungs of all cases by inoculation of tissue cultures. This virus was non-pathogenic for animals; it behaved in tissue cultures just like typical measles virus and was closely related to it by serological tests. In an accompanying paper Anna Mitus and co-workers[5] describe four other cases of pneumonia after attacks of clinically evident measles. All the children were being treated for leukaemia. A typical giant-cell pneumonia was present in the lungs of the two fatal cases, and measles virus was recovered from the lungs. It may therefore be concluded that at least some cases of giant-cell pneumonia are definitely due to measles virus.

Enders and his colleagues offer no explanation of why there was no rash in the first three cases they describe, but there did seem to be some difference between the pathogenesis of the virus infection in these chronically ill children and in normal children. For one thing the virus persisted in the respiratory tract long after the onset of the disease, and for another the blood contained little or no antibodies even after the illness had gone on for several weeks.

THE KINKED INNOMINATE VEIN

During the past decade physicians have paid more attention to the jugular venous pulsation. Unfortunately a number of observations have been made on the external jugular veins. These may be an unreliable guide to the pressure in the right side of the heart. They may be valved or trapped in the fascia of the neck, and unless free pulsation is observed the height of the venous pressure in them is not a good guide to the assessment of heart failure. Observation of the deep jugular veins, with the patient reclining at an angle of 45 degrees, should give an accurate reflection of the diastolic pressure in the right ventricle.

Pulsation is sometimes seen to be freer or more distinct in the left deep jugular vein than the right, though of course the pressure in both deep jugular veins is equal. Now Shirley Smith[1] has drawn attention to the syndrome which he describes as the kinked innominate vein. By this he means distension without pulsation of the left deep jugular vein, the right displaying free pulsation as is normally seen. He states that he has seen this on scores of occasions and describes five cases, with illustrations. He has also measured the venous pressure in both antecubital veins in such patients and finds that it is higher in the left than the right. This led him to believe that the obstruction of venous flow must be within the chest and involve the left innominate vein. He produces convincing evidence that the compression of this vein is due to an enlarged and high aortic arch.

This observation fulfils two purposes. First, it draws attention to the fact that unilateral venous engorgement of the neck is due to impaired venous inflow into the right side of the heart, and, of course, is not associated necessarily with any cardiac abnormality. Secondly, in the absence of a mediastinal mass it is a helpful sign in the diagnosis of a high and rigid aortic arch. It is probably the increased rigidity of the aorta which is responsible, for it is a sign which is not observed in association with the high, freely pulsating aortic arches of patients suffering from coarctation of the aorta. If pulsation is easily felt in the suprasternal notch, and if in addition there is a "kinked" left innominate vein, the diagnosis of increased aortic rigidity can be strongly suggested. All Shirley Smith's patients had, in addition to atherosclerosis, hypertension to a moderate or severe degree.

CHLOROTHIAZIDE AND HEPATIC COMA

The place of chlorothiazide and similar preparations in the management of fluid retention due to congestive cardiac failure is now firmly established. The powerful effect on excretion of potassium has proved something of a disadvantage, but this can be overcome by intermittent therapy and by giving potassium supplements. Nevertheless the original trials[1] revealed that patients with severe liver disease were particularly sensitive to hypokalaemia and were liable to develop hepatic coma, especially when a good diuresis occurred. The mechanism of this effect has now been studied in greater detail by Professor Sheila Sherlock and her colleagues.[2] Half the fifteen cirrhotics who were given 2 g. chlorothiazide developed neuropsychiatric symptoms, and it was noteworthy that in all but one the drug had produced an effective diuresis. Potassium excretion was augmented, and this resulted in a fall in serum potassium, which was accompanied by a rise in the alkali reserve, in the *p*H of the blood, and in the level of ammonia. By an ingenious if laborious method of measuring the rhythmic activity of the brain in daily electroencephalograms, these workers detected a slowing of mean frequency which coincided with the onset of neuropsychiatric symptoms. It remained to determine

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whether mental deterioration was directly related to hypokalaemia, and two observations strongly support such a view. Relief of symptoms followed the giving of potassium supplements, while three patients with severe cirrhosis deteriorated when placed on a diet low in potassium.

The way in which hypokalaemia affects cerebral metabolism in liver disease is not clear. Mental disturbances do not commonly accompany hypokalaemia in association with other pathological states. In cirrhosis, however, chlorothiazide may aggravate a pre-existing cellular depletion of potassium brought about by such factors as ascites, diarrhoea, and malnutrition. On the other hand the respiratory alkalosis and increase of ammonia in the blood which accompany hypokalaemia occur in hepatic coma from other causes, though it is doubtful whether they are primarily responsible for the symptoms. Whatever the mechanism, chlorothiazide must be added to the growing list of substances which are potentially dangerous in liver disease—a list that includes protein, methionine, ammonium salts, and acetazolamide. Some of these are valuable therapeutic agents when used in the right circumstances. Similarly with chlorothiazide. In the present study, for example, a large dose was given intentionally, and it may be that small, intermittent doses will prove to be safe. Even so, potassium supplements are probably obligatory. It would be unwise to condemn out of hand the use of these substances in liver disease for the further reason that recent work[8] has suggested that chlorothiazide can lower the portal venous pressure in patients with oesophageal varices.

PENICILLIN AND MENTAL UPSET

Mental disturbance as a direct side-effect of treatment with penicillin must be extremely rare. But injections of procaine penicillin have on occasion been followed almost immediately by an hour or two of acute distress and several days of exhaustion.[1 2] Hysterical behaviour, fear of impending death, and possibly hallucinations were noted. Such upsets occurred after one of a series of injections which were later continued without further reaction, and it was thought that accidental intravenous injection of procaine penicillin was the cause. There seemed reason to blame the procaine rather than the penicillin.

Recently a similar delirious reaction has been reported after taking oral tablets of probenecid penicillin.[3] In two of the cases mental disturbance followed the first dose, and when after recovery a further dose was given the psychotic episode recurred. In the third case, a girl of 11, the prescribed dose was without ill effect, but the accidental ingestion of a double dose produced mental symptoms in half an hour, continuing for about four hours.

Probenecid, like procaine, is usually regarded as a safe drug, though in enormous overdosage both have previously been reported to produce cerebral disturbance.[4] Both are substituted benzoic acid derivatives. Unusual sensitivity to them does not seem to have the characteristics of an anaphylactic response, and in the absence of other explanation it is reasonable to speculate on a biochemical mechanism such as that of vitamin dependence. Individuals exist, but rarely, who need more of some particular vitamin than do the rest of us. As long as they have a rich intake they are well, but on a lower diet still adequate for the mass of the population they develop specialized symptoms of vitamin deficiency. Thus a few children are epileptic unless given about ten times the normal intake of pyridoxine,[5 6] and a very few others develop mental symptoms if they do not get plenty of nicotinamide.[7] Probenecid is believed to interfere with the function of coenzyme A, which contains the vitamin pantothenic acid, and is responsible for a variety of metabolic steps, including the synthesis of acetylcholine. It is possible that the few who react to probenecid with mental symptoms are vitamin-dependent individuals, existing on the borderline of a vitamin deficiency.

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ANNUAL MEETING IN NEW ZEALAND

The B.M.A. is proud of its firm links with the Commonwealth and of the kinship which unites so many doctors in lands so far apart. New Zealand is about as distant from the United Kingdom as it is possible to be, yet the medical relationship between the two countries could hardly be closer. It is therefore entirely fitting that an eminent son of New Zealand, Sir Arthur Porritt, who succeeds the Duke of Edinburgh as President of the B.M.A. in a month's time, will himself induct another New Zealander, Mr. Douglas Robb, into the office of President when the B.M.A. holds its Annual Meeting in Auckland next February.

This is the first time the B.M.A. has gone so far afield, though it has met four times in Canada and once, in 1935, in Australia. The meeting will be held in conjunction with the Biennial Conference of the New Zealand Branch of the B.M.A. The provisional programme published in this week's *Supplement* shows how attractive the meeting is going to be on both the scientific and social sides. But, in addition, the meeting offers a wonderful opportunity to see New Zealand and its people in the most agreeable circumstances possible. For those who can spare the time to visit Australia also, there are to be special functions arranged by the Australian State Branches.

If anyone has any doubts about making the long journey to New Zealand, then surely Mr. Douglas Robb's letter at p. 1563 will convince them that here is an opportunity not to be missed. He quotes a line from Horace which has for long been a caption on the cover of the *New Zealand Medical Journal*. The same work, as if written to describe the joys awaiting the visitor to New Zealand, goes on to mention the delights of sailing, and continues, "Quod petis hic est"—"What you seek is here"—a classical travel slogan. Those who wish to test it by attending the New Zealand Meeting should write forthwith for an application form to the Executive Officer, B.M.A. House, Tavistock Square, London, W.C.1.

Drug Treatment of Disease

ADMINISTRATION OF DRUGS BEFORE ANAESTHESIA

BY

WILLIAM W. MUSHIN, M.A., M.B., B.S., F.F.A.R.C.S. F.F.A.R.A.C.S.

Professor of Anaesthetics, Welsh National School of Medicine, University of Wales

The administration of drugs of some sort before an anaesthetic is an almost universal practice. Yet the reasons for it do not always appear to be clear. In many cases the drugs given are unnecessary because they confer no benefit on the patient and needlessly complicate the subsequent anaesthetic. In others the wrong drug is chosen, and the desired effect is not achieved.

Aims of Premedication

(1) To prevent undesirable side-effects of the anaesthetic on various organs. These include those on the salivary glands, on the heart, and on the alimentary canal.

(2) To make the induction and maintenance of anaesthesia more easy. The induction of anaesthesia in an unpremedicated, lively, robust patient, even without the added complication of emotional upset, may be a very different affair from that in a similar patient who has had a suitable combination of sedative and antisialogogue drugs.

(3) To prevent undesirable autonomic reflex responses to stimuli arising mostly from the operation area.

(4) To lessen pre-operative anxiety, fear, and emotional tension in general. This has been put last, not because it is less important than the others, but because a real need for this effect is not nearly so commonly apparent to-day as it was in years gone by. The anaesthetist cannot help, to a certain extent, identifying himself with his patient and imagining that he must be fearful and hence require sedatives or hypnotics. A very careful objective assessment of each patient should be made and depressant drugs ordered only when either emotional stress is obvious or when the patient spontaneously asks to go to sleep in his bed or at least to be made sleepy, or to have no memory of the induction of anaesthesia.

The last three objectives are usually achieved by the same drug. In general, anaesthetists are coming to the view that sedative drugs should be given only when there is a clear need for them and not as a routine. Certainly every patient must be regarded as an individual. The increasing skill of anaesthetists, the gradual disappearance among the public of the fear of anaesthesia, and the wider range of anaesthetic drugs, all combine to make heavy sedation of the patient less necessary. The growing custom of gaining the confidence of the patient by personal contact cannot be too highly praised. A pre-operative visit is often as effective as an injection of morphine.

Factors Affecting the Dose of Pre-anaesthetic Drugs

Age and Weight.—The effect of drugs in general and of sedatives in particular is closely related to the metabolic activity and general excitability of the patient. The dose per unit weight is therefore scaled down with increasing age. The metabolism of old people is low; in the young it is high. At birth, the dose per unit weight for a particular effect is greater than that for the adult. The dose/weight ratio rises until between the ages of 6–10 it is about 25% more than the adult ratio. It then gradually drops until at the age of 20 the individual is considered an adult, and needs the "average" or "usual" dose. In practical terms, therefore, the dose per pound of body weight for an adult must be increased by approximately 25% for a healthy child of, say, 6 years in order to achieve the same effect.

Body weight is clearly a most important factor affecting dosage. Most of the classical cautions regarding the use of sedative drugs in children probably stem from too large a total dose being given in the past. Thus, in the case of morphine, 15 mg. (gr. ¼) for an adult of 10 stones (63 kg.), is a dose: weight ratio of gr. 1/40 per stone (0.2 mg. per kg.). If an infant is given morphine on this scale, the effect produced will be a little less than that seen in the adult because of the difference in metabolism already pointed out.

Temperature. — Febrile patients need slightly increased doses to show the same effect, because of the rise in metabolism. This need must be balanced against any suspected lowered resistance to drugs due to the toxaemia of the disease.

Pain.—Pain is an indication for analgesics like morphine rather than hypnotics like the barbiturates. The administration of a barbiturate to a patient in pain may lead to uninhibited reflex reaction to the pain in the form of restlessness. Post-operatively, even though the patient is not awake, restlessness may be so marked as to be a problem to the nurses, and it may even introduce the risk of injury and, in certain circumstances, of haemorrhage. The child after tonsillectomy exemplifies this state of affairs.

Emotion.—The relation between the dose of sedative drugs and emotional stress needs no emphasis.

Physical States.—Patients vary a great deal in their general state of health. The anaemic, listless girl of 18 presents quite a different problem to her robust, games-playing sister. The former may need no sedative drugs at all or at most a relatively small dose. If a "normal" dose is given to such a patient severe depression may follow and the patient perhaps need resuscitation.

Anaesthetic to be Administered.—The pre-anaesthetic drugs form part of the anaesthetic procedure, and in ordering them the anaesthetist must bear in mind their possible interaction with the anaesthetic. For example, powerful respiratory depressants are best avoided before anaesthetics like ether, with which good spontaneous respiration is essential if deep anaesthesia is to be achieved.

SEDATIVES AND ANALGESICS

Morphine

A preparation of opium is still the commonest form of sedative before an anaesthetic. Its powerful effects in relieving pain, removing fear, producing euphoria, and relaxing tension account for its popularity. The reduction in reflex excitability facilitates the induction of anaesthesia. However, respiration is depressed, and, partly as a result, this is accompanied by circulatory depression. Respiration becomes slower and shallower. The dose is all-important. In a healthy adult of 10 stones (140 lb., 63 kg.) 10 mg. (gr. 1/6) of morphine usually produces adequate analgesia and euphoria without serious respiratory depression. For the best and safest effects it is important that morphine or an opiate, if given hypodermically, should be injected about 1½ hours before the proposed time of operation, so that the peak depressant effect is present or has just passed when anaesthesia is induced.

Morphine has certain other undesirable side-effects. Nausea and vomiting are more common than is generally believed. Morphine has a direct effect on the medullary vomiting centre. This action is exhibited to an even more striking degree by morphine's close relative, apomorphine. The incidence post-operatively of nausea and vomiting due to morphine is probably at least as high as 20%. When administered apart from operation and anaesthesia, nausea and vomiting is uncommon in patients in bed, but it occurs frequently if they are ambulant. An incidence as high as 40% for nausea and 16% for vomiting is reported. There is no doubt that morphine given as premedication increases the tendency of patients to vomit post-operatively. If this factor in post-operative vomiting is to be avoided, morphine must be replaced by some other sedative which does not have this effect.

Other undesirable side-effects of morphine are its spastic action on the gastro-intestinal tract leading to constipation and its spastic effect on the bronchial musculature. Substitutes should therefore be considered for patients with, for example, biliary colic or bronchial asthma.

Two preparations of opium need special mention. Papaveretum (or "omnopon") contains all the opium alkaloids and is standardized to contain half its weight as morphine. The adult dose of 20 mg. (gr. ⅓) therefore contains 10 mg. (gr. 1/6) of morphine. It is believed by many to be less liable to produce nausea and vomiting because the papaverine which it contains counteracts some of the gastro-intestinal spastic action of morphine. Since the other opium alkaloids are also sedatives, 20 mg. (gr. ⅓) of papaveretum has about the same sedative effect as 15 mg. (gr. ¼) of morphine.

"Nepenthe" is a proprietary liquid preparation of opium containing morphine. This preparation was originally intended as a somewhat elegant alternative to tinct. opii, to be taken by mouth. It has, however, become much favoured for administration to children by hypodermic injection, perhaps because the widely used dosage scale of "one minim per year" is easy to remember. Nepenthe by injection as a pre-operative sedative for young infants cannot be recommended. It is difficult to measure one or two minims let alone a fraction of a minim with accuracy, and errors in measurement of perhaps over 100% are inevitable. In addition, children of the same age vary widely in weight and physical state. The difficulty of estimating and measuring the dose of this preparation for an infant of under 1 year is therefore obvious. The author has seen a variation in effect in infants, ranging from apparently none to obvious overdose, leading to a comatose infant with pin-point pupils. When morphine is to be administered to infants it is better to use the alkaloid itself and to calculate the dose from the body weight, by using the formula gr. 1/40 per stone (0.1 mg. per lb., 0.2 mg. per kg.).

Pethidine

This is a synthetic compound which differs from morphine in that it has some atropine-like effects. Clinically the effects on the intestinal tract are less spastic, and on the bronchi even relaxant. Its analgesic effects are particularly marked when the pain arises in certain hollow viscera such as the uterus. Given in equipotent doses to morphine, however, it appears to depress respiration less. Pethidine is often combined with some other sedative drug to provide an analgesic component to the mixture.

Barbiturates

These drugs are sedative or hypnotic, the result depending on the dose, but have no analgesic power. Those with a medium duration of action—for example, quinalbarbitone ("seconal," pink capsules), or pentobarbitone ("nembutal," yellow capsules), are commonly given by mouth for this purpose. At least two or three hours should be allowed for absorption from the alimentary canal and for the onset of the peak effect. This time can be shortened if the capsule is pierced. These drugs are valuable for children. They fall asleep and usually have no memory of going to the operating-theatre or of the induction of anaesthesia. For an adult, an oral dose of at least 3 gr. (200 mg.) of either of these is needed if sleep is desired, and this may be combined with a small dose of morphine if pain is present. For children under 6 or 7 stones (80–100 lb., 38–44 kg.) in weight, a dose of gr. ½ per stone (2 mg. per lb., 5 mg. per kg.) will usually induce sleep if the child is left quiet. A disadvantage of the oral route is that fear may delay the desired effect by inhibiting intestinal activity, including emptying of the stomach.

Increasingly, barbiturates are being administered to children by the rectum. This method is particularly valuable in children and infants because of the ease of administration and certainty of action. The dosage scale is 20 mg. of thiopentone per pound body weight (45 mg. per kg.) (or 1 g. for 50 lb.). 1 g. is dissolved in 50 ml. of tap water and 1 ml. is administered for each pound body weight (2.2 ml. per kg.) by means of a syringe and small catheter. Sleep comes on rapidly within a quarter of an hour and passes off during the following hour. The manufacturers of "pentothal" now offer a ready-mixed emulsion of thiopentone in multi-dose disposable syringes. Detachable rectal applicators enable the same syringe to be used for more than one patient.

Phenothiazine Derivatives

Some of these drugs are very effective as sedatives before anaesthesia. They have a powerful potentiating effect on the general anaesthetics, and it can be expected that reduced doses of the latter will suffice. Two examples, though there are others, are promethazine ("phenergan") and chlorpromazine ("largactil"). In

proper doses these drugs relax the patient and make him calm and comfortable without depressing respiration. If left alone, patients tend to go to sleep but are easily aroused and then are mentally clear. Induction and maintenance of anaesthesia are considerably facilitated. They also have important anti-emetic effects and are valuable in patients who fear or have a predisposition to post-operative vomiting. Nevertheless, there are disadvantages. Their effects are prolonged and may last many hours. Circulatory depression with a varying amount of hypotension is not uncommon, especially with chlorpromazine. Pallor is often striking.

A satisfactory combination for an adult is promethazine 50 mg., pethidine 50 mg., and atropine 0.6 mg. intramuscularly 1½ hours before anaesthesia. Chlorpromazine may be substituted for the promethazine in doses of 12–25 mg. intramuscularly.

Other Sedatives

Many other sedative drugs, some old and some new, can be used successfully before anaesthesia. These include such old friends as chloral hydrate, paraldehyde, and even aspirin. Of the newer drugs, mention can be made of two codeine derivatives—dihydrohydroxycodeinone (oxycodone) pectinate ("proladone") and dihydrocodeine bitartrate ("D.F.118"). These are potent long-acting analgesics. Another drug which has received many enthusiastic reports is methylpentynol ("oblivon"). This is a sedative advocated for children, in whom it induces calmness and mild euphoria before such operations as tonsillectomy. It has a wide margin of safety—for example, a child of 5 to 8 years receives 2–3 teaspoons of the elixir, of which each teaspoon contains 250 mg. of methylpentynol.

Control of Secretion

All anaesthetics, with perhaps the exception of nitrous oxide and halothane, cause an increase in salivary secretion during induction and light anaesthesia. In any case normal secretion is not abolished. If not checked, the foaming of saliva may cause serious respiratory obstruction, and not only interfere with the smooth course of the anaesthetic but may put the patient's life in hazard. It is now almost universally regarded as essential that every patient, except those having the briefest of anaesthetics, should receive a drug which reduces the secretion of saliva.

Atropine is the one most commonly given for this purpose. A dose of 0.6 mg. (gr. 1/100) in an adult depresses salivary secretion by about 50% and in practice this effect is sufficient. Hyoscine ("scopolamine") is an alternative to atropine, and, being slightly more potent, the dose is reduced to 0.4 mg. (gr. 1/150). Both atropine and hyoscine depress the central nervous system and causes a varying amount of drowsiness. Hyoscine is more active in this respect and noticeably potentiates the effect of other sedative drugs.

The depression of salivary secretion is even more important in children than in adults; the larynx and trachea are so small that a small quantity of secretion may seriously impair respiration. The increased metabolism of the child indicates a higher dose-to-weight ratio than an adult. A combination of these two factors explains why in the past such apparently excessive doses of atropine or hyoscine for a child were given; it is not because infants, as some imagine, have a peculiar tolerance for atropine. Nevertheless, overdosage of infants with atropine must be avoided, since it depresses sweating and disturbs the heat-regulating mechanism; this may lead to dangerous overheating in these young subjects. The following guide to atropine dosage may be found useful:

Age in Years	Dose
Newborn	gr. 1/400 (0·16 mg.)
Up to 1	,, 1/300 (0·22 ,,)
1–	,, 1/200 (0·32 ,,)
2–	,, 1/150 (0·43 ,,)
Over 4	,, 1/100 (0·65 ,,)

An important effect of atropine and hyoscine is to depress vagal nerve endings in the heart and produce tachycardia. This is believed to give some protection against the vagal stimulating effect of anaesthetics like chloroform, trichloroethylene, cyclopropane, and halothane. Atropine also causes bronchodilatation and helps to prevent bronchospastic reflexes during anaesthesia. Some protection against visceral reflex responses during abdominal operations is also given.

SPECIAL PROBLEMS

The Chronic Alcoholic and the Drug Addict

These patients are generally tolerant of sedative drugs, and considerably larger doses than usual may be required to produce a satisfactory effect. Generally the best way to produce tranquillity in such patients is to give them a suitable dose of what they are accustomed to.

Pregnancy

Unless the patient is at or near term she may be treated like any other woman. However, if premedication is connected with operative obstetrics, sedatives are best avoided. If they have to be used, the effect on the baby must be considered. All the drugs already described cross the placenta rapidly, and within minutes circulate in the foetal blood in the same concentration as in the mother's. The baby at the time of birth will therefore be nearly as sedated as the mother at that moment. To avoid the danger of serious respiratory depression of the baby, the dosage of the sedative must be smaller than usual, and it must be given either more than 3–4 hours before the expected delivery or, in the case of morphine and similar drugs, with an antidote. Nalorphine (N-allylnormorphine) or levallorphan ("lorfan") may be combined with morphine or pethidine. A ready-mixed combination with pethidine is available and is known as "pethilorfan," in which the proportion of the antidote, levallorphan, is such (1:80) that, while serious respiratory depression is prevented, much of the analgesic and sedative properties of pethidine is retained.

Pulmonary Disease and Respiratory Obstruction

Care should be taken in administering sedatives to patients with these diseases. Their very life may depend on their ability to make a maximal breathing effort. Any reduction in this by sedatives may have disastrous consequences.

Sensitivity from Other Drugs

Patients receiving certain drugs as treatment for a co-existing disease may be specially sensitive to sedatives. Examples are antihistamines, tranquillizers, hypotensive drugs, and disulfiram.

TRANSLATING FROM RUSSIAN

BY

D. H. SMYTH, M.D., M.Sc., Ph.D.

Professor of Physiology, University of Sheffield

Though it is essential for all scientists to keep in touch with work published in languages other than their own, this task probably presses more lightly on English-speaking workers than on others. This happy state of affairs is due to two main factors (apart from the large contribution made by British scientists themselves): (1) the enormous output of American research, and (2) the at least temporary decline in the importance of German as a scientific language and its replacement by English in the Scandinavian and other countries. In recent years, however, the problem of reading foreign languages has been raised in a new form by an increasing awareness of the number of publications in Russian; and, even if the Russian achievements in biology and medicine are less spectacular than in some other fields, the problem of Russian translation is likely to receive increasing attention.

There would seem to be three methods of tackling this problem: (1) the development of electronic translation, (2) the creation or expansion of a class of professional translators as distinct from working scientists, and (3) the provision of better facilities for the scientist who wishes to read Russian himself. There can be little doubt that electronic translation must be at least part of the solution, even if it does not completely replace the human translator, and the next five or ten years will probably see great advances in this direction. A good deal has already been done, and Booth, Brandwood, and Cleave (1958) have published an account of work done at the Birkbeck College. Recent numbers of the *L.L.U. Translation Bulletin*, published by the D.S.I.R., also give an account of work of this kind. A Russian project for machine translation from French into Russian was started in 1954, and the first translated sentence appeared in June, 1956. (It is an interesting speculation whether work on electronic translation, quite apart from its technical value, might not throw some unexpected light on fundamental problems in linguistics.) The expansion of the professional translator class is also likely to be a partial solution to the problem of Russian translation; but this is not a very easy solution, as in many scientific fields understanding the subject-matter may be just as formidable a task as understanding the language in which it is written. The third possibility is for the scientist to learn Russian, just as a generation ago he learned German. Without going into all the problems of either the professional or the amateur translator, one of the needs of both is a good Russian–English dictionary, and the publication of a Russian–English medical dictionary by Jablonski and Levene* makes it pertinent to review the present resources available.

The Russian translator is restricted to dictionaries meant for general use, many of which are excellent of their kind, or to the very small number of technical dictionaries or compilations of Russian words of which I find Callaham's (1947) *Russian–English Technical and Chemical Dictionary* the most useful. Carpovich's (1958) *Russian–English Biological and Medical Dictionary*, with which I am less familiar, is also valuable, but its production in a photo-offset edition does not make for easy use. How does Jablonski and Levene's dictionary compare with these?

**Russian–English Medical Dictionary*, by Stanley Jablonski, and edited by B. S. Levene. Academic Press Inc., New York, 1958. 88s.

Criteria of a Dictionary

The value of a dictionary can be judged by the following criteria: (1) its clarity—that is, kind of type, size of print, quality of paper; (2) the accuracy of the meanings given; (3) the amount of information given in addition to the actual meanings of the words; and (4) the range of words chosen for inclusion. It must be made clear that these criteria are considered here, perhaps somewhat rashly, from the point of view of the amateur translator rather than that of the professional linguist. As regards clarity, Jablonski and Levene's work leaves nothing to be desired, and this question of clarity is of special importance in dealing with the Cyrillic characters in which Russian is printed. A comparison with Carpovich's book will convince the reader of the truth of this statement. There also seems no reason to doubt the accuracy of the meanings, and the very occasional words—for example, impuberal, non-tumoral, meninx—which look slightly strange would presumably look less so to American eyes.

The amount of information given in addition to the meanings of the words is a matter on which there is considerable room for difference of opinion. From the translator's point of view the extra linguistic information is usually not of great value; it makes the entries longer and more complicated and may add greatly to the size of the book. Even information on the aspect of Russian verbs, though useful, is often not indispensable in technical translation. There is therefore no serious complaint that Jablonski and Levene offer only the meanings of the words and an indication of the part of speech. There is, however, one piece of information which adds nothing to the length of the entry and is of the greatest value to the translator, and that is the stress or accent on the Russian words. Even if one is not attempting to acquire a speaking knowledge of Russian, one hopes to remember a number of the words looked up and hence to be able to look up fewer words with more experience. Most people fix words in the memory by remembering sounds (even if these are not the correct sounds) rather than visual images. If, therefore, stresses have to be given to different syllables it seems a great pity not to learn the correct stress from the beginning. The absence of stresses is a major defect in this dictionary, as it is also the most important defect in Callaham's dictionary. Many of the non-technical dictionaries are adequate in this respect.

The range of words included is perhaps the most important matter, and the one thing the translator desires more than any other is to find all the words he needs in one volume. It is undoubtedly far easier to use one larger dictionary than two smaller ones, and for scientific translation portability is not very important. The present dictionary falls down in this respect as it is meant specifically to supply only technical words of medical interest. It is true the authors indicate in the preface that the dictionary is intended to be used only in conjunction with a non-technical dictionary, but the fact remains that Callaham's dictionary, though only a little larger, gives most of the words, technical and non-technical, likely to be needed in dealing with medical and biological literature.

Types of Technical Words

But if a dictionary is meant to supply technical words it is perhaps fairest to judge it from this point of view. There are two types of technical words likely to be met with in Russian: (1) words of Slavonic origin, and (2) words of Western origin. The first group create the real problem. They are totally unfamiliar to the English reader, and they may not be included, or at least their technical meaning not included, in ordinary dictionaries. The value of a dictionary in this respect can only be judged by using it, and in a very short trial the following absentees were noted: исчерченный (striated, referring to muscle), подрытый (undermined, referring to the edge of an ulcer), вставочный (intercalated or internuncial, referring to nerve fibres), посев (culture, referring to micro-organisms), тяж (tract or column in neurology), неживой (non-living). Under бляшка the meaning motor end-plate was not included, and осумкование is rightly given as meaning encystment, but the additional important meaning "encapsulation" referring to sensory end-organs was not found. These are all words likely to be frequently encountered, and it is precisely words of this kind which give most trouble to the translator. It is also unlikely that I happened to note all the important omissions in a few preliminary trials.

The second group of Russian technical words, and fortunately a very large one, comprises those borrowed from Western science. Once the Cyrillic alphabet has been mastered these words present almost no difficulty, provided the reader is familiar with the English equivalents—for example, адреналин (adrenaline), антибиотик (antibiotic), гликоген (glycogen), комплемент (complement), перифлебит (periphlebitis), пикротоксин (picrotoxin), рефлекс (reflex). It is these words which the compilers of the dictionary have concentrated upon, with what might seem to be a considerable waste of time and effort. On almost every page at least half the words listed and often more could be guessed without any difficulty by anyone with only the smallest experience of Russian, but with a technical knowledge of the subject. It is true that words of this kind would be more useful to the professional translator with little technical knowledge, but, even so, more concentration on the Slavonic technical words would surely have been far more useful.

Another serious criticism is the system of listing many of the adjectives and adjectival expressions. These are given as sub-entries under the nouns with which they might be associated, and may or may not be given in their own alphabetical position. The authors explain the system in the introduction, in which they say, "Compound terms are alphabetized by nouns with secondary arrangement of modifying adjectives." This means in practice that the adjective криминальный (criminal) is not given under K but is given as a sub-entry under аборт (abortion). Similarly, описательный (descriptive) appears as a sub-entry under анатомия (anatomy) and has no entry of its own.

In other cases multiple entries are given. Thus межреберный (intercostal) is given at least five times, as a sub-entry under артерия (artery), нерв (nerve), мышца (muscle), and пространство (space), as well as under its own entry. It is very difficult to understand the advantage of this system, and it is presumably tacitly assumed by the compilers that the adjective "criminal" will only be used to qualify the word "abortion," and the adjective "descriptive" to qualify only the word "anatomy."

Problem of Abbreviations

Russian scientists, like their colleagues elsewhere, use a large number of abbreviations, and these can present formidable problems to translators. The dictionary makes a very real effort to cope with this problem by including a very large number of abbreviations, and this is undoubtedly a very useful feature. I have found no obvious omissions on looking up a few familiar abbreviations, and the zeal with which abbreviations have been tracked down by the authors is surely indicated by ЗАКВОДГЕО, which stands for Transcaucasian Branch of the All Union Scientific Research Institute of Water Supply, Canalization, Hydraulic Structures, and Hydrogeological Engineering.

While this dictionary will fill a number of gaps in our present needs it still fails to provide the complete answer to the translator's prayer, and if there are any enterprising organizations or individuals with such a laudable project in mind they should be encouraged to proceed with their work in the knowledge that they have not yet been forestalled.

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Nova et Vetera

MANIPULATION OF THE SPINE

In a long paper published in four numbers of the Norwegian Medical Association's journal[1] Dr. Eiler H. Schiøtz, an industrial medical officer in Oslo, has discussed manipulation of the spine from a medical and historical point of view. The paper gained him the Lederle award. He found that diseases of the locomotor system accounted for about 17% of all absentees from work, and in studying the prevention and treatment of these diseases he became interested in the history of manipulations of the spine.

In this paper he gives a fascinating account of the manipulation-traction treatment of the spine from the earliest known sources of information up to the most recent publications on the subject. The detailed description of the most ancient methods is well illustrated. The great mixture of sense and superstition which marks the treatment in many countries is presented in a most readable way. Bone-setters, osteopaths, and chiropractors are exposed in a factual manner. The doctor's opinion on manipulation during the last decade is also described. The author makes an effort to explain the basis of how manipulation works, and lists indications and contraindications for this treatment and how it has been carried out.

The paper is an extremely thorough and sober study of the problem. One can only agree with the author that, although manipulation of the spine is sometimes indicated, too often exact indications are missing because no exact diagnosis has been established. We are in what he calls "a vertebral no-man's-land." The two hundred and fifty references would be most useful for any student of this problem.

J. AGERHOLM.

[1] Schiøtz, E. H., "Manipulasjonsbehandling av columna under medisinsk-historisk synsvinkel," *T. norske Laegeforen.*, 1958, **78**, 359, 429, 946, 1003.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Stilboestrol Diphosphate
"Honvan" (Ward, Blenkinsop).

Chemical Composition.—Stilboestrol diphosphate is a phosphorylated synthetic oestrogen formed by the substitution of a "phosphate" complex for the hydroxy grouping at each end of the stilboestrol molecule.

Pharmacology.—Unlike stilboestrol itself, stilboestrol diphosphate is highly soluble in water and can be administered intravenously as well as by mouth. Given by either route it remains pharmacologically inert until broken down by the enzyme phosphatase, with the liberation of free stilboestrol. Thereafter its pharmacological and oestrogenic properties become those of stilboestrol, the intensity of effect being modified by the proportion of active oestrogen liberated and its distribution in the body.

Therapy.—Stilboestrol diphosphate has been evolved for the treatment of prostatic cancer on the assumption that stilboestrol not only indirectly diminishes androgenic stimulation of the growth, but also exerts a direct cytotoxic effect on the tumour cells themselves. The liberation of free stilboestrol from the phosphorylated compound is stated to occur mainly in prostatic carcinomatous tissue, where concentrations of phosphatase are often high and the requisite *p*H is present. Theoretically this should result in a local concentration of active stilboestrol at the primary and metastatic sites, thus promoting an enhanced direct effect on the tumour. Proportionately the amount of free stilboestrol passing into the general circulation should be reduced, with a corresponding diminution of pharmacological and oestrogenic side-effects.

Evidence supporting these assumptions is at present inconclusive, for, whereas the results of biological assay give some indication of a concentration of stilboestrol in prostatic tissue, tracer studies have so far failed to show any corresponding increase in radioactivity. If carbon-labelled stilboestrol diphosphate is given intravenously, a large proportion of the dose is found to be excreted rapidly in the urine, while much of the residue appears to be conveyed to the reticulo-endothelial system and liver, presumably in unchanged inert form. It can, however, be postulated that the last two sites may serve as reservoirs from which supplies of oestrogen are subsequently released into the general circulation.

Stilboestrol diphosphate has been particularly recommended in cases resistant to ordinary stilboestrol therapy or complicated by troublesome side-effects such as gynaecomastia, nausea, vomiting, and oedema. While its efficacy in controlling the malignant process has been extolled in some centres, there is no unanimity of opinion in this respect, and much to suggest that any apparent superiority over conventional treatment is due to the large quantities administered. In this connexion the preparation may well be indicated as a temporary form of treatment when a rapid response is urgently required—e.g., severe metastatic pain or urinary retention. The recommended dosage is 500 mg. in saline intravenously on the first day followed by injections of 1,000 mg. a day for six days, thereafter reducing to 250–500 mg. two to three times weekly (or 100–200 mg. three times a day by mouth).

Toxic and Other Side-effects.—Rapid intravenous injection of stilboestrol diphosphate is usually followed by transient severe burning pain in the sacral and perineal regions. This evidently does not denote a local prostatic reaction, since similar discomfort is experienced by the female subject. To obviate this disturbance, administration by slow intravenous drip is advised.

Oestrogenic side-effects are said to be slight, but nevertheless gynaecomastia and oedema certainly occur, though nausea and vomiting after oral administration are seldom troublesome. Oestrogens are believed to be metabolized in the liver, and prolonged high dosage should be avoided in view of the possibility of hepatic damage and failure.

Contraindications.—Stilboestrol diphosphate is contraindicated in cases with previous hepatic damage and should be administered cautiously to patients suffering from cardiac insufficiency with oedema.

N.H.S. Basic Price.—5-ml. ampoules, 10 for 32s.; 100-mg. tabs., 100 for 32s.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

B.M.A. Meeting in New Zealand

SIR,—I thank you for the opportunity of reminding members of the British Medical Association that its 129th Annual Meeting is to be held in Auckland, New Zealand, in conjunction with the Biennial Conference of the New Zealand Branch, from February 6 to 10, 1961.

Never before has the Association ventured so far to visit so few, but in this country we are sensible of the honour and determined to do all we can to make it a happy and memorable occasion. We hope many of our friends and colleagues from the Old Country and from Canada, Australia, and other parts of the Commonwealth will make the trip, and give us the opportunity on our home ground to show how much we have valued our associations and the help given when it has been our turn to travel abroad. These are days when we can fly through the air with the greatest of ease, and we hope that the air will be thick with you passing south as the godwits fly north for their summer holidays in Siberia.

A full week is being planned both for work and for play. The scientific programmes will appear in due course in this journal. Close at hand you will be able to see the harbour and the bridge and try the salt water and the breezes on the Hauraki Gulf. For the seagoing the Mako shark and the marlin will be waiting; for the lake and river men, Rotorua, Taupo, and the forests, to say nothing of the glow-worms and the geothermal power station; for those who will visit the South Island, the lakes, the mountains, and the glaciers; and all in an environment of almost total social security. We look forward to this occasion as a reunion—under new skies certainly—which will bear out the truth of the *New Zealand Medical Journal's* regular caption, "*Coelum non animum mutant qui trans mare currunt.*"
—I am, etc.,

Auckland, New Zealand. DOUGLAS ROBB.

Bornholm Disease and Herpangina in W. Scotland, 1959

SIR,—The summer and autumn of 1959 in Western Scotland were characterized by the usual seasonal increase in poliomyelitis-like illnesses. Laboratory investigations of hospital patients showed almost complete disappearance of poliomyelitis virus but considerable prevalence of Coxsackie virus infections.[1 2]

The absence of any obvious outbreak of Bornholm disease at this time suggested that the predominant strains of Coxsackie virus might be unusually neurovirulent—most of those isolated came from patients with aseptic meningitis or paralytic disease.

In an attempt to explore this possibility further, a simple questionary was sent to 55 general practitioners who were already collaborating with this laboratory or had attended a recent postgraduate course at Ruchill Hospital. Information was asked about both Bornholm disease (caused by Coxsackie B viruses) and herpangina (ulcerative pharyngitis, caused by some Coxsackie A viruses). Replies were received from 30 practitioners. Not all the answers were complete, but the information supplied is summarized in the following table.

Prevalence	Bornholm Disease	Herpangina
Unusually high	4	3
Average	14	14
Unusually low	7	6
Number of cases seen:		
0	13	13
1–3	7	4
4+	5	7
Mean cases per practice	2·3	3·7

No evidence was found of generally raised incidence of either Bornholm disease or herpangina. Comments on the questionary pro formas suggested that herpangina was not well recognized as a specific entity distinct from other ulcerative oral conditions, and was almost certainly less prevalent than the figures suggest. It may be noted that the Coxsackie viruses most frequently isolated in this laboratory in 1959 were types B5 and B2, which are known to cause Bornholm disease, and type A7, which has not been reported to cause herpangina.

Despite the incomplete information available, the results of this inquiry are compatible with a hypothesis of increased neurovirulence of Coxsackie viruses in this area in 1959. The situation merits continued attention in relation to evaluation of poliovaccination. I am grateful to my colleagues in general practice who provided the information for the above analysis.—I am, etc.,

University Virus Laboratory, Ruchill Hospital, Glasgow, N.W. N. R. GRIST.

REFERENCES

[1] Duncan, I. B. R., and Sommerville, R. G., *Hlth Bull. (Edinb.)*, 1960, **18**, 1.
[2] Grist, N. R., *Brit. med. J.*, 1960, **1**, 344.

Osteoarthritis of the Hip

SIR,—I would like to comment on the letter (May 7, p. 1427) by Dr. W. K. Dunscombe, who apparently is seriously handicapped in dressing and performing his personal toilet after arthrodesis of the hip. Dr. Dunscombe attributes this difficulty to the failure of orthopaedic surgeons to emphasize the importance of post-operative rehabilitation, to a failure to teach post-operative rehabilitation to orthopaedic registrars, and to a tendency "to dismiss airily the points raised in the sanctuarial calm of an editorial office or a consultant's couch."

With the tendency "to dismiss airily" on the consultant's couch I agree, but the suggestion that orthopaedic surgeons commonly neglect post-operative rehabilitation clearly indicates that Dr. Dunscombe has missed the whole point of my article (March 19, p. 821) on the future of the surgery of the hip-joint. It is true that there are many patients dragging themselves about the country at the present moment with serious disabilities after arthrodesis of the hip, but there are also many others who perform athletic feats almost indistinguishable from those of normal persons. To suggest that the difference lies in the quality of the physiotherapy received by these two categories is simply putting back the clock. In 1960 we are, I hope, a long way ahead of the old idea that it is the physiotherapist who saves the patient after the orthopaedic surgeon has perpetrated an ill-conceived procedure resulting in delayed union and joint stiffness. In the future surgery of the hip-joint the quality of the surgery will be inversely proportional to the size of the physiotherapy department.

In the centre devoted to the study of hip-joint surgery which we have established at Wrightington we frequently succeed in achieving osseous union between four and eight weeks after operation. The problem is now to discover how to achieve this in every case. Osseous union taking place in an arthrodesis at this speed dispenses with the need for the old-style physiotherapist. With the new look in hip surgery the physiotherapist of the future will still be at the right hand of the surgeon, but she will get her results merely by assisting the patient to take the first steps and, which is even more important, by dispelling the fears and uncertainties which beset the patient during the many hours when the surgeon is absent. A knee which will not flex through a range of 110 degrees after arthrodesis of the hip is the responsibility of the surgeon who designed the operation; it has very little to do with the patient and the physiotherapist.—I am, etc.,

Wrightington Hospital, Nr. Wigan. JOHN CHARNLEY.

SIR,—Dr. W. K. Dunscombe (May 7, p. 1427) has hit the (non-orthopaedic) nail on the head when bringing to notice some of the dismal complications of operations on the hip. Having developed this acute condition myself nearly three years ago, I have taken great pains to follow up operation cases, and I have still to see one who can reach his own foot to put on his sock. What does he do if he has to stay in a hotel alone? While admiring orthopaedic surgeons for their well-intentioned efforts, I would give heart to the non-interference brigade by telling them that great improvement will take place if only early use of two (adjustable) walking-sticks, or elbow crutches, is taken. A large amount of body weight is taken off the legs and transmitted through the arms. I believe that sticks is a dirty word in orthopaedic language, but this is the only way, and, after crawling for about a year on two sticks, I can now manage nicely on one, and I can put on that sock and drive a car, while pain is less and even mobility returning.

It is satisfying to know that one can get through a good day's work with minimum inconvenience.—I am, etc.,

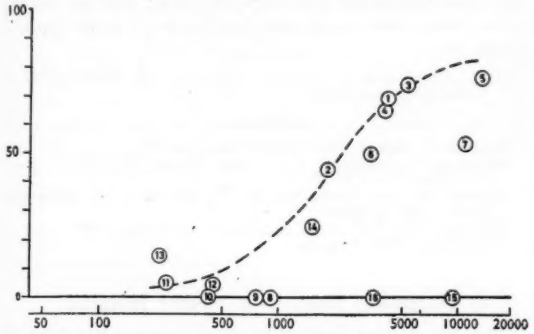
Blackpool. J. E. SWINBURNE-JONES.

"Imferon"

SIR,—Your leading article,[1] based on the paper of Haddow and Horning,[2] which was inspired by the observations of Richmond,[3] has led to the banning of the iron-dextran preparation imferon, a preparation widely used therapeutically for intramuscular injection. As a consequence of the following considerations essentially different conclusions may be drawn from the experi-

mental data of Haddow and Horning and Richmond than the authors themselves and the author of the leading article journal do.

Haddow and Horning conclude that the cancerogenic effect of imferon is decided primarily by the absolute amount administered, and only secondarily, if at all, by the relation of this to the body-weight. As the following representation will show, this conclusion seems not to be based on the facts given in the publications.



Abscissa: tumour frequency in %. Ordinate: dose mg. Fe per kg. body weight, logarithmic scale. The number of the plots refer to the table.

In the Graph it is attempted, on the basis of figures from the papers of Richmond and Haddow and Horning, to relate the relative dose of iron used in experiments with rats and mice to the frequency of tumours observed. As no quite definite weights are given for the animals in the experiments it is arbitrarily supposed that the weight of a rat is 250 g. and that of a mouse 33 g. On this basis a total dose of Fe per kilo body-weight is estimated (see Table). This dose is used as abscissa in the diagram. The ordinate is the percentage of animals with tumours. The greater part of the points in the diagram fit neatly on a dose-response curve as indicated in the diagram.

The points on the right part of the curve (1–5) represent various doses of ordinary imferon, those on the left part (11, 12) standing for soluble organic ferrous salts. Only one point (13), representing ferrous gluconate, is situated decidedly above the curve—i.e., showing a greater tumour frequency than expected from the curve. Below the curve, showing less than "normal" tumour frequency, the points 6 and 7 represent poorly absorbable iron-dextrans, the point 14 iron saccharate ("ferrivenin"). Metallic iron (15) and dialysed ferric oxide (16) appear to be entirely without cancerogenic effect, the same possibly being the case for two organic ferric compounds (8, 9).

TABLE

No. in Diagram	Author	Experimental Animal	Dose Fe mg./kg.	No. of Animals	Tumours	Tumour Frequency %	Preparation
1	Richmond	Rat	4,000	23	16	70	Imferon
2	,,	,,	1,900	40	22	55	,,
3	Haddow and Horning	,,	5,200	30	24	75	,,
4	,,	Mouse	3,900	15	10	66	,,
5	,,	,,	13,500	23	18	78	,,
6	,,	,,	3,300	20	10	50	Iron-dextran, poorly absorbable
7	,,	,,	10,800	13	7	54	
8	,,	,,	900	20	0	0	Ferric citrate
9	,,	,,	750	20	0	0	Ferric salicylate
10	,,	,,	400	20	0	0	Iron ascorbate
11	,,	,,	240	20	1	5	Ferrous sulphate
12	,,	,,	420	20	1	5	Ferrous lactate
13	,,	,,	215	20	3	15	Ferrous gluconate
14	,,	,,	1,560	20	5	25	Ferrous saccharate
15	,,	,,	9,600	20	0	0	Metallic iron
16	,,	,,	3,360	20	0	0	Dialysed Fe_2O_3

As seen in the Table, these experiments have been performed with experimental groups of roughly speaking the same size, regardless of the total dose of iron. It is obvious that in order to construct the left part of the curve with the same reliability as the right part, far greater experimental groups will be needed. One fact stands out—namely, that rather moderate doses of absorbable iron compounds subcutaneously applied are able to cause the development of tumours in mice. The smallest total dose given in the experiments can be estimated to 3–4 times the normal iron content of the whole animal. On the other hand, no evidence whatever seems to indicate that iron as imferon or the iron-dextran complex itself is more cancerogenic than other iron compounds.

It may therefore, in accordance with Dr. L. Golberg (March 26, p. 958), be supposed that the tumours at the injection site observed after iron injection in experimental animals are caused by the repeated local traumata from the massive injections combined with the oversaturation of the organism with iron. In my opinion, therefore, the only consequence of these experiments ought to be that great caution must be recommended regarding the dose of iron injected subcutaneously or intramuscularly, possibly even intravenously, in man.—I am, etc.,

J. G. A. PEDERSEN.

Biological Laboratory,
Aktieselskabet Pharmacia,
Copenhagen-Vanløse, Denmark.

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Care of the Old

SIR,—Your leader-writer who wrote "Care of the Old" (April 23, p. 1261) appears to have a singularly poor understanding of the purposes and functions of the medical services of local authorities. Briefly, they are to promote the general level of health, to protect the public against disease, to provide supporting services such as ambulances, midwives, nurses, etc., and supplementing personal medical services where these are not provided either by general practitioners or by hospitals.[1]

One of the duties of a medical officer of health is to inform himself as far as practicable respecting all matters affecting the public health in the district and be prepared to advise the local authority on any such matter. After a number of careful surveys[2 3 4] it has been ascertained here, and also in a number of other places, that there exists a vast mass of disability in older people. A great many people who have these disabilities do not know they have them and hence do not go to doctors about them. Thus there exists a problem in community health which needs a solution. This solution will not be found so long as your leader-writer writes: "If they (domestic help and home-nursing services) are not adequate, money might be better spent in improving them than in the creation of elaborate municipal preventive clinics for the elderly, which at best will attract only the energetic and least vulnerable

old people, and at worst could usurp another function of the family doctor."

The local authorities employ doctors to do individual medicine in the supplementary services because if this work was not done by local-authority doctors it would either not get done at all or done only to a very small extent. This is the case with the school-health service, the infant-welfare service, the immunization service, and the antenatal service. No general practitioner as part of his terms of service is required to carry out routine examinations like insurance examinations for nothing; and the truth is that if the school-health and infant-welfare services were left to be done voluntarily by general practitioners, then only the most conscientious parents would bring their children to be examined, and then often in circumstances where the practitioner has little interest in the work, has few facilities, and inadequate auxiliary assistance. The vast majority of children would thus get no attention at all.

Similarly the disabilities of older people will not be discovered, or remedied, or prevented from getting worse unless the local authorities undertake this job as part of their supplementary service. How can it usurp the function of the family doctor when the family doctor does not undertake it at present, and is not likely to add to his burden the routine examination of hundreds of older people when he need not?

Consent has been given to try out experimental clinics for older people in a number of places. Experience in them has shown that even "the energetic and least vulnerable old people" have plenty of things wrong with them, and a great deal can be done to make them fitter and happier and less of a burden on those around them. It is quite unfair of your leader-writer to condemn outright local-authority clinics; surely there is a place for all types of service—hospital, local authority, and practitioner—in the care of older people. The main aim of the clinic is to discover disabilities in the early stage and to try to prevent them from getting worse. As opposed to this, an old person will wait to be referred to the hospital geriatric unit after a breakdown has occurred.

No one denies the wonderful work done in treating and rehabilitating these older people in the geriatric unit. The fact remains, however, that there are not enough of such units, and certainly not enough staffs to cope with the existing gravely ill and chronically ill patients; nor are there likely to be for many years to come. Neither are the existing medical services dealing adequately with the mildly unwell older person. Again no one denies that the patient's family doctor is the keystone for his well-being, and to whom he turns for treatment, advice, and if need be reference to hospital. But how can the average busy practitioner with a surgery full of people and a long visiting-list be expected to listen to the circumlocutions of a mildly unwell older person and do a full clinical examination for the detection of all disabilities? He just hasn't got the time.

The aim of the local-authority prevention clinic is to give any older person who cares to attend a full clinical examination, together with diagnostic procedures and tests. It is not the aim to deal with those who are ill, for that is the province of the practitioner or geriatric unit. The clinic will then report the findings of this examination to the practitioner; give the person advice about health matters, diet, habits, social amenities, extra assistance, glasses, and supply cheaply supplementary foods. The time of the practitioners is saved; they are pleased with the help they get from this supplementary service; the older people are pleased because they get excellent attention and time devoted especially to them; and surely we as taxpayers should be pleased if we are saved expenditure on hospital and residential services for old people who might otherwise be fit and independent.

Again it is not true to say that, "The shortage of home helps for the elderly is serious and almost universal. Local authorities seem reluctant to vote funds for these purposes, yet the discharge of an elderly fit person from hospital all too often depends entirely on the availability of a home help." In my area the authority is most far-seeing and will spend every penny needed to provide essential—but not extravagant—home-help services. The incidence of illness goes up and down; only last week we actually had home helps to spare. No person need be retained in our local hospital for lack of a home help, but you must remember that they have to be paid for, and frequently their services are refused when an applicant learns the cost, however low; and we cannot force home helps on to people who won't have them.—I am, etc.,

J. MADDISON.

Health Department,
Teddington, Middlesex.

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Disturbing Noise in a Mental Hospital

SIR,—In a recent paper in the *Journal* (December 5, 1959, p. 1247) Dr. Cecily Statham described a study of patients' reactions to noises at the Royal Northern Hospital, London. Since noise is a persistent problem in all large institutions, especially those in which patients may spend long periods of time, it seemed worth while to repeat her procedure in a large hospital for mental patients. We were interested in learning whether the kind of noises that affect patients in a general hospital would (*a*) be found in a mental hospital, and (*b*) bother the patients in a mental hospital. Interviews were carried out with 123 patients who were asked if they were bothered by noise; the nature of the noise; and whether the noise occurred during the day or night. The information was related to the number of people sleeping in the same room as the respondent. Interviews were carried out by nurses on three types of wards: admission; active treatment; and chronic psychotic. Most of the patients slept in large dormitories with from 20 to 50 other people, while a few shared rooms with two or three patients, and only two had single rooms. The population on the various wards ranged from 40 to 120. The length of hospitalization of the patients varied from a few days to 30 years. This hospital also differed from the Royal Northern in terms of location, being set on the outskirts of a small prairie city (population 8,000) where, because of its spacious grounds, the only traffic is that going to and from the hospital.

The interviews showed that 42% of the patients reported that they were bothered by noise (as compared with 50% found by Dr. Statham). Male and female patients complained with equal frequency, while patients who slept in small bedrooms were bothered more than people who slept in larger bedrooms or dormitories. However, people sleeping in dormitories have more complaints of noises at night. Generally speaking, patients were bothered to an equal extent by day and night noises.

By far the most frequent source of noise, constituting two-thirds of all complaints, was other patients. The only other frequent sources were radio and television. Only one patient mentioned the hospital staff as a source of disturbing noise. The quietness of the hospital exterior is reflected by the fact that only two patients

complained of noises outside their own ward. These noises were the wind and construction going on in an adjacent part of the building. Our results paralleled those of Dr. Statham in that patients in smaller bedroom units (single rooms in her survey) complained of more disturbing noises than did patients who slept in dormitories. In both general and mental hospital, disturbing noises came predominantly from other patients. Both studies showed a similar number of patients with complaints about noise, and the sexes were equally prone to bothersome noises.

The most striking difference between the mental hospital and the general hospital is the frequency of external noise; while this was the source of 25% of the complaints in the general hospital, it comprised only 4% of the complaints here. This is undoubtedly due to the different locations of the two hospitals.—We are, etc.,

ROBERT DEWAR.
ROBERT SOMMER.

Psychology Department,
Saskatchewan Hospital,
Wyburn, Canada.

Undescended Testicle

SIR,—This correspondence on the subject of incomplete descent of the testis is futile in the absence of facts and figures. The school medical examinations seem the ideal source for these figures, but the school medical officers seem unable to recognize the retractile testis and their figures are useless. Cannot a surgical clinic supply some figures?

The usual child with rectractile testes referred by the school medical officer presents little difficulty. Inspection of the patient lying on a couch reveals that both testes are in the scrotum, and if the fingers and thumb of the left hand press the spermatic cords against the pubis the testes can safely be palpated. The testis in the superficial inguinal pouch is more difficult. Since 1938 I have interpreted Mr. Denis Browne's teaching as follows: a testis in the superficial inguinal pouch may be ectopic or incompletely descended: if it can be pushed into the neck of the scrotum it is incompletely descended, if not ectopic. But this test is not as clear cut as one would like. How far down is the neck of the scrotum? I have heard a professor of surgery confidently diagnose bilateral ectopic testes in a lad of 13; yet one testis descended spontaneously within the next three months.

Nevertheless, I have continued to try to distinguish the ectopic from the incompletely descended testis. As the years have gone by, I have been disappointed by the number of boys who have reached the age of 14 with their "incompletely descended" testes still in the groin. When the American work on testicular biopsy was published I searched my records but found little reassurance, although the numbers were too small to have any significance. But the children's hospitals should be able to produce significant figures. I invite Mr. Denis Browne (May 7, p. 1428) to ask his registrar to go through the records and let us have the figures. Ignore the testis which is obviously retractile. We would like to know how many testes are classified as ectopic at the first visit and how many as incompletely descended. When the latter are followed, at what age do they descend? If these figures have already been published I apologize, but beg for the reference. Perhaps Mr. W. M. Dennison (April 30, p. 1360) might care to let us have the figures for Glasgow?—I am, etc.,

Pontefract. JAMES A. RHIND.

Infantile Scurvy

SIR,—I have recently read with interest the article by Dr. M. K. Strelling on infantile scurvy (March 5, p. 701). We have been interested in this problem, having seen 14 cases of severe infantile scurvy from Nova Scotia in a period of five and a half months. These infants ranged in age from 5½ months to 13 months except for one mentally retarded infant of 27 months of age. In all cases except one the intake of vitamin C was negligible, owing to ignorance on the part of the parent regarding proper feeding habits. In one case, however, the infant was receiving 50 mg. of ascorbic acid a day and developed clinical and radiological evidence of scurvy at 5½ months.

The reports by Whelen *et al.*[1] and Grewar[2] would indicate that infantile scurvy still exists in Canada. Whelen *et al.* reported that, of 79 cases of infantile scurvy, 80% received no vitamin-C supplement, but 20% by history had received some form of vitamin C. The possibility therefore exists that infantile scurvy may occur while the infant is receiving vitamin C in amounts generally considered adequate to prevent scurvy. We have considered the possibility of vitamin-C-"conditioned" scurvy. By this term we mean that the ingestion by the pregnant mother of large amounts of vitamin C may "condition" the infant *in utero* to requiring much larger doses of vitamin C after birth. If perhaps 100 to 300 mg. were not available the symptoms of scurvy might occur while the child was receiving the recommended 25 to 30 mg. per day. The one case of scurvy that had been receiving "adequate" vitamin C was of interest because the mother had ingested approximately 300 to 400 mg. a day of vitamin C from about the fifth month of pregnancy. We are now carrying out experiments in guinea-pigs that may support or reject our theory of vitamin-C-"conditioned"-scurvy.

Support for the suggestion that "conditioned" scurvy may occur is found in the publication by Hunt *et al.*[3] regarding vitamin B_6. These authors described a newborn infant who had recurrent convulsive seizures and progressive mental retardation. The infant's seizures were controlled by the administration of 2 mg. of vitamin B_6. The mother had received large amounts of vitamin B_6 during her pregnancy, and the authors suggested that the infant may be "pyridoxine dependent." Unquestionably nutritional qualitative deficiencies still exist in the "lands of plenty," and must be considered as the possible underlying cause of such common complaints as irritability, lethargy, vomiting, pallor, and hyperthermia.—I am, etc.,

W. A. COCHRANE.

Department of Paediatrics,
Dalhousie University,
Halifax, Nova Scotia.

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2 Grewar, D., ibid., 1958, **78**, 675.
3 Hunt, A. D., jun., Stokes, J., McCrory, W. W., and Stroud, H. H., *Pediatrics*, 1954, **13**, 140.

Acute Urinary Infections

SIR,—I was very interested to read Professor D. A. K. Black's very practical lecture on "The Treatment of Renal Diseases" (March 5, p. 667). It was his approach to the fourth syndrome—viz., acute urinary infection—that interested me most. He remarked that the family doctor should have open access to a clinical laboratory. This cannot be too strongly emphasized if proper

treatment is to be carried out in these and other conditions and so relieve the Hospital Service of unnecessary patients. On the other hand, if specimens of urine are sent from all patients complaining of dysuria, etc., the laboratories would be overwhelmed; at the same time, if the urine of all the patients with dysuria, etc., is not examined, there would be many cases of acute or chronic pyelonephritis missed. To get over this difficulty a procedure must be instituted that is simple for the patient to carry out and not time-consuming for the doctor. With this in mind I have developed the following routine.

If the patient is a male he is instructed to pass a mid-stream sample into a sterile bottle. In the case of the female she is instructed to boil a little jug or funnel with a bottle and cork. Before coming to the surgery with the sample she has a bath, or if no home bath is available a hip-bath. After she has dried herself she passes water into the sterile jug, then puts it in the sterile bottle and corks it immediately. If there is no infection such a sample will be sterile on culture. If the urine is crystal clear there is obviously no urinary infection; if turbid a flamed platinum loop is put into the bottle and a drop of urine is put on a clear microscope slide and examined under the 1/6 lens. If pus cells and not crystals are seen there is a urinary infection. With experience the infecting organism can be recognized sufficiently well to be a guide to treatment, as it is usually *Bact. coli.*

A first attack is treated by a course of sulphonamides as suggested by Professor Black. The big proportion of the cases return in a week with a clear urine and symptom-free. A further check after a few weeks usually gives a clear urine. Return cases and cases that do not clear up have their urine sent to the laboratory. These are a small proportion of all the cases.—I am, etc.,

Batley, Yorks. A. FULLERTON.

Demand for Medical Care

SIR,—The Nuffield Provincial Hospitals Trust publication by Mr. Gordon Forsyth and Dr. R. F. L. Logan is dealt with very kindly by a *B.M.J.* reviewer (April 23, p. 1257). The authors, however, do not deal equally kindly with doctors in general practice, and on these they produce adverse verdicts from very controversial premises and by obscure processes of reasoning.

As an example, on page 106, the writers say, "It is all very well in theory to cast the general practitioner as the leader of the new advances in preventive medicine because he has the best chance of undertaking pre-symptomatic detection. But has he the necessary skill to take up the challenge? The death rate from coronary thrombosis in middle-aged men, with anticoagulants available, suggest that he has not." This vague piece of writing raises several questions. Who has cast the general practitioner as the leader of the new advances in preventive medicine? How can any doctor prevent death from coronary thrombosis in middle-aged men he may not have seen for years? Is it established that the use of anticoagulants will prevent or cure coronary thrombosis? Some eminent cardiologists think not, and point out that the evidence produced by the protagonists of these drugs is marginal, and such as has been often produced by enthusiasts in the past in favour of various medical treatments later discredited. Death amongst middle-aged doctors, and particularly amongst those in general practice, from coronary disease is uncomfortably frequent in spite of the availability and often the use of anticoagulants. If such deaths cannot be prevented among medical men it is not surprising that they occur among non-medical men, and it is quite unreasonable to blame the lack of skill of the general practitioner for their occurrence.

The authors also say that one of the reasons why the stay in British hospitals is longer than that in American hospitals is the failure of the general practitioner to integrate the hospital and domiciliary services. This is absolute nonsense, and it is difficult to see how such a conclusion can be drawn by the writers without incurring a charge of prejudice. The main reason for the difference is that in Britain a hospital bed costs nothing and in America it costs a lot, even for subscribers to contributory schemes for medical care.

Other comments by the writers on general practice show an equal lack of logic and of balance, but I will not trespass on your space to deal with them. I would only say that the criticisms produced in this booklet can have no useful effect whatever. Indeed, they could do a great deal of harm. They have already been summarized and commented on uncritically in an editorial in a national newspaper not usually distinguished for the wisdom of its comments on the Health Service, but they have aroused very little comment. This seems to show that the public has the good sense not to take them seriously.

Frequent criticisms of doctors in general practice have been made over the past eleven and three-quarter years by many people, most with an axe of some sort to grind and with no knowledge or experience of general practice. A few of these criticisms have been justified in some cases, but, whether justified or not, all have been borne with a patient shrug. Here, however, this is not enough, and a faint squeak of protest seems justified in the hope that future critics may produce more convincing evidence before indulging in such sweeping condemnations as are contained in this booklet by Dr. Logan and Mr. Forsyth.—I am, etc.,

Bath. W. B. S. CRAWFORD.

A New Exanthem?

SIR,—In your correspondence column (March 19, p. 877) under the heading "A New Exanthem?" appears a description by Dr. Bernard Peck of a febrile condition in children associated with a rash of "retiform morphology" that is variable in nature. I wish to commend Dr. Peck for the very detailed and most informative description which he gives of the condition about which he is concerned. Dr. Peck's description was so accurate that it quickly brought to mind a condition about which the following comments have been recorded:

"The rash frequently assumes garland or lace-like configurations . . . and is characterized by a curious series of evanescences and recrudescences. . . ."[1]

"The disease usually appears as a bright flush on both cheeks, as if they had just been slapped, with few prodromal or accompanying symptoms . . . within 24 hours, the facial lesions have spread to assume the butterfly distribution characteristically seen in lupus erythematosus; within 48 hours the eruption appears on the arms and upper trunk to spread later to buttocks and legs. As the rash ages, it becomes coalescent, and fades centrally to form multiple iris, large serpiginous, or "lace-like" lesions."[2]

"All cases presented the typical pattern—bright red cheeks . . . followed in 24 to 48 hours by a delicate erythematous

mottling of the skin on the volar surfaces of the forearm, on the extensor surfaces of the upper arms and thighs, and, less frequently, on the chest and abdomen."[3]

"These resemble measles and rubeola, presenting a rosy-red maculopapular eruption beginning on hands and arms . . . and rapidly spreading . . . as more people became affected, the rash assumed a bizarre and polymorphous appearance. Even in the same person, it varied from a morbilliform distribution on face and limbs to huge coalescent patches of a bright red hue. . . ."[4]

Another description of an outbreak of a disease similar to that described by Dr. Peck appears in a German medical periodical and is abstracted in the *J. Amer. med. Ass.* (1959, **169**, 1239).

The disease about which the above notations have appeared in the medical literature is erythema infectiosum; also called fifth disease.—I am, etc.,

Seaside Memorial Hospital, Long Beach, California. GEORGE X. TRIMBLE.

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[2] Moore, W. F., *Hawaii med. J.*, 1956, **16**, 35.
[3] *Morbidity and Mortality* (Weekly publication of U.S. National Office of Vital Statistics), March 31, 1956.
[4] Grimmer, H., and Joseph, A., *A.M.A. Arch. Derm.*, 1959, **80**, 283.

Delay in the Third Stage

SIR,—However careful antenatal care may be, there seems to be no way of predicting when there will be delay in delivery of the placenta, and a "retained placenta" usually involves the patient in the hazard of general anaesthesia plus the shock caused by manual removal. As general anaesthesia is now one of the chief causes of obstetric deaths, any effective method for avoiding it is obviously of great value; particularly in domiciliary practice, when both a highly skilled anaesthetist and really good facilities (e.g., for suction) are often lacking. It is therefore most unfortunate that the Brandt–Andrews method of delivering the placenta is not more generally known. One wonders why the method is not taught in medical schools, or, indeed, to midwives, for it seems to be the least traumatic of any method, and is certainly more comfortable for the patient than "fundal pressure." Can it be that many have not even troubled to see if the method is any good because for so many years pulling on the cord has been regarded as an "obstetrical sin"?

The advantages of the Brandt–Andrews technique are: (1) It is easy to learn. (2) No anaesthetic or special equipment is needed. (3) It causes minimum discomfort to the patient. (4) It does not cause "shock" (cf. Credé's method). (5) In the event of failure, no harm has been done, and a manual removal can still be carried out in the usual way. Since learning the method some 18 months ago I have had occasion to use it several times, so far with complete success. The method was described recently in your columns by Kimbell.[1]

The method can be modified according to the circumstances. For example, if called to a post-partum haemorrhage, with the placenta still in the uterus, one can ask the midwife to give ergometrine at once, and then one can proceed with the Brandt–Andrews method on arrival. Someone can be sent to call for the flying-squad, if the patient is likely to need blood, but usually there is a marked improvement in the patient's shocked condition once the placenta has been delivered.—I am, etc.,

Bridgwater, Somerset. P. M. ELWIN.

REFERENCE

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Inoculation Technique

SIR,—I feel that I must cross swords with Dr. David Hooker, of Truro, over the contents of his letter (April 30, p. 1362). One would not expect a case of infective hepatitis after injecting with an improperly sterilized needle. One would expect homologous serum jaundice—a different kettle of fish. The incubation period of infective hepatitis is nearer thirty days than six weeks.

Dr. Hooker feels that, as the recruits left his care six weeks after the last injection, the follow-up period was complete. In fact, as the incubation period of the virus of homologous serum jaundice is 60–120 days, his follow-up period had hardly begun. The fact that 1,000 recruits who had been vaccinated with lymph blown (presumably orally) along the tubes did not develop secondary infection is surely not an argument in favour of using such a method. In the practice of medicine, one should strive to attain the ideal. Because we can get away with murder, this surely does not condone our committing it.—I am, etc.,

Manchester, 11. C. B. COHEN.

SIR,—Dr. David Hooker (April 30, p. 1362) saw no jaundice developing within 39 to 67 days after his 4,000 injections. As the incubation period of homologous serum jaundice is about 100 days this is hardly surprising.—I am, etc.,

Pathology Laboratory, Essex County Hospital, Colchester. J. W. NICHOLAS.

SIR,—How very ingenious we are in our efforts to be hygienic! What is wrong with a sterile 2-ml. syringe and a hypodermic needle for expelling lymph from a tube for vaccination? The only disadvantage to my mind is that it is not quite so easy to insert the needle into the open end of the tube, with the eyesight of middle-age, as it was on qualifying.—I am, etc.,

Leeds, 8. ANNE HOSKER.

SIR,—The correspondence arising out of the criticism of an immunization session as represented on T.V. has been most interesting. No one would doubt that the ideal method would be to use a separate sterile syringe and needle for each injection, but there would be comparatively few doctors zealous enough to adopt this procedure when performing any appreciable number of inoculations, for two reasons: (*a*) the time involved; and/or (*b*) the extra number of syringes required.

I quite commonly inoculate 60 people in one session. Using six 10-ml. syringes, but a separate needle for each injection, the session lasts one hour from the start of sterilization to signing the last document. Using the ideal method and 10 syringes can take anything from 2 to 3 times as long.

A solution to the problem of devising a safe method of inoculation which would be widely used would be to place a non-return valve to prevent back-flow of a patient's serum into the syringe. If it is not technically possible to incorporate a valve in a needle then it could be incorporated in an adapter fitting between the needle and the syringe. Such a unit would necessarily have to operate under a small-pressure differential, and whether it should be sterilized for each injection or for use with each syringe could be determined in the laboratory or in the light of clinical experience. I imagine the former

technique would be safer and many of these units would have to be available. Would not a valve similar to the Spitz–Holter be appropriate ?—I am, etc.,

Stow-on-the-Wold, Gloucestershire. S. J. STRONG.

Imipramine and "Reactive" Depression

SIR,—A booklet entitled "Reactive Depression" has recently been widely circulated to the medical profession by the manufacturers of the drug "tofranil" (imipramine). The statement is made that "tofranil for clinical and practical reasons provides an important aid in the home treatment of reactive depression which has to be treated much more frequently than endogenous depression by the general practitioner." This suggests that the booklet is aimed at the general practitioner and that he is encouraged to treat reactive depressions at home by tofranil. There follows a description of clinical features alleged to be those of reactive depression and which are said to include such symptoms as "a kind of stupor in which all capacity to act or even move seems to be lost," "earnest self-reproaches or accusations against others," "the patients often lose interest in their surroundings and become apathetic," "physical complaints become more common and include disorders of digestion, difficulty in swallowing, heart complaints, headache, and sexual disorders."

Even the most junior psychiatrist will realize that such symptoms are not those commonly understood as reactive depression but usually indicate a depression of more severe or even psychotic nature and which, although sometimes initiated by an external factor, is endogenous in form. But the psychiatrically uninformed or unwary general practitioner may be led into believing that such depressions may be regarded as minor in nature because they are called "reactive." This may result in the failure to recognize serious psychiatric illness, treatment being lightly undertaken and unfortunate consequences sometimes ensuing.

If manufacturers take it upon themselves to offer clinical instruction in addition to a description of their drugs, they have a responsibility to make sure that the information they offer is accurate. Imipramine, along with certain other anti-depressive drugs, has a valuable place in the treatment of depression when administered after careful evaluation of the nature of the illness. It is, however, recognized by many leading authorities that the more severe depressive illnesses respond more rapidly and satisfactorily to E.C.T., and that to delay such treatment may sometimes lead to unexpected suicidal disaster. To label some severe depressions "reactive" and encourage the general practitioner to treat them at home by drug therapy would be both misleading and dangerous.—I am, etc.,

London, W.1. BRIAN ACKNER.

Administration of Oxygen

SIR,—On reading the article by Dr. Mary Catterall and Mr. Michael Snow (April 23, p. 1254) on "The Polymask as a Means of Administering Oxygen," I was surprised to see that no reference was made to the original publication by Burns and Hall on this subject.[1] This gave measurements of alveolar oxygen concentrations obtained with the mask, and also drew attention to the same difficulties which arise in its use. The main purpose of the recent article appears to have been to remind us that incorrect use will result in unsatisfactory functioning.—I am, etc.,

Department of Anaesthetics, Guy's Hospital, London, S.E.1. R. J. VALE.

REFERENCE

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Side-effects of Phenelzine

SIR,—Dr. J. Clarke's letter on the side-effects of "nardil" (phenelzine) (April 16, p. 1204) is most interesting. I would add to his list the interesting one of drowsiness (as of course already reported in the Canadian literature). In the group of depressive illnesses I have used the drug with, this complication comes second only to mild unsteadiness. These were the only two side-effects I have encountered in a group of about 30 patients.—I am, etc.,

Severalls Hospital, Colchester. H. JACOBS.

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Shoes for Children

SIR,—Dr. Catharine Hollman's excellent survey of retail shoe shops of Ealing in 1958 (March 5, p. 719) highlights a number of problems common to shoe shops in all parts of the country. Her report would have been of even greater interest to many in the shoe trade had some practical suggestions been added to show how the pressing problems of economic service, training for skilled fitting service, and adequate supplies in reasonable variety of good shoes for children could be solved by co-operative action.

It appears from Dr. Hollman's survey that four-fifths of Ealing shoe shops sell children's shoes and that the child population of 34,000 (under 15 years of age) divide their custom among 39 shops. On average this provides 872 customers per shop for children's shoes—assuming that all parents prefer to shop in their own neighbourhood.

What sort of fitting stock should be expected from these shops ? From size 2 infants to size 8 in the senior range there are 39 sizes and half-sizes. If three fittings are to be provided as a minimum range in each half-size we have 117 pairs of shoes in stock to fit the first customer. Suppose we are content with two colours and three styles —lace, bar, and sandal—we then have 702 pairs in stock. If Dr. Hollman could have told us the true incidence of size and fitting demand likely to arise from the 34,000 children of Ealing, we could then apply a proper ratio of size duplication to our stock of one pair of a size, so that our stock of 702 pairs would probably rise to about 2,000 pairs. If all the 39 shops of Ealing repeated such a stock there would then be 78,000 pairs of shoes available to supply 34,000 children.

It may well be that Dr. Hollman's suggestion regarding children's specialist shops is one answer to this economic problem, but such an idea could only be carried out provided that the following conditions obtained: (*a*) All other shoe shops and other sources of shoe supply would have to agree to discontinue selling children's shoes. (Possibly seven specialist shops would be ample for 34,000 children.) (*b*) The retail margin of profit for children's shoes would have to be adjusted to provide an *amount* of profit comparable to that applying to adult shoes offered with highly trained skill and comprehensive stocks. (*c*) That parents, educational, and medical authorities would co-operate to ensure that children of school age and under are *compelled* to wear only correctly fashioned and correctly fitted shoes. Then, and then only, can the shoe trade tackle

the very serious position which has arisen since children have been allowed to disregard school uniforms and to ape adult shoe fashions.

Training of shoe-fitting assistants at short courses by manufacturers can never be of much value except to impart technical knowledge, and must for the present depend upon the manager's interest and ability. When the economics of providing skilled fitting services have been settled there will be a call for high-grade training courses. These can be provided by technical establishments in conjunction with trade organizations as soon as the need and demand arise. It is one of the prime objects of the newly established Society of Shoe Fitters to establish these facilities and to provide the high standard of shoe services Dr. Hollman would approve.—I am, etc.,

F. H. GEORGE,
President, Society of Shoe Fitters.

London, W.2.

The Blood–Brain Barrier

SIR,—The claim referred to in your annotation (April 23, p. 1263) on the blood–brain barrier that the existence of such a "barrier" has now been proved[1] should not be too literally accepted. There has always been a great deal of confusion over the blood–tissue relationships of the central nervous system, due largely to the widespread belief that these are governed for all substances by the permeability properties of some unique membrane interposed between blood and brain. If there were such a structure it is difficult to see why its properties should be so unpredictable. Hypotheses that blood–brain penetration of a substance depends on its lipid solubility and/or its charge are only partly true; and probably only serve to emphasize the similarities in this respect between brain capillaries and those of other tissues. The similarity of behaviour of ions of opposite charge, the unimpeded penetration of glucose (the tissue's main energy source) in spite of its water solubility, and the almost complete failure of cholesterol, itself a lipid, to enter the adult brain, are only some of the notable exceptions which challenge the validity of such hypotheses. There is every reason to believe that the blood–tissue relationships of the brain reflect rather than limit its metabolism, just as in other organs, and it is unfortunate that "it has become traditional to discuss a part only of these relationships in a somewhat negative fashion under the title of the blood–brain barrier,"[2] whereas "much depends on exclusion or assimilation by the cerebral cells themselves."[3]

Davson and Spaziani[1] showed that P.A.H., iodine, and sucrose occupied only between one-seventh and one-third of their estimated available chloride space in the brain after two hours' continuous intravenous infusion, whereas in the case of muscle the whole of the chloride space was occupied by the same substances within six minutes. When the tissues were compared *in vitro*, however, there was a similar fast rate of uptake into brain as into muscle. This is the basis of the claim that "there *is* an appreciable extracellular space, entry to which is impeded by a blood–brain barrier."[1] Much rests, however, on the validity of the *in vivo*:*in vitro* comparison. Pieces of brain were 2.5 mm. thick and were compared with undamaged diaphragm 1.5 mm. thick. Brain is extremely susceptible to metabolic deprivation compared with other tissues, and is considerably more fragile in the fresh state. Variations in oxygen tension, for example, penetrating the more deeply situated cells deprived of their normal capillary supply, would not produce such serious permanent consequences in muscle as in brain, which is so much more restricted in its choice of metabolites and so much more dependent on their continuous supply. Normal gradients across cell membranes depend greatly for their maintenance on cell vitality, and in this way the brain is strictly not comparable with other tissues *in vitro*.

Morphologists are quite clear that even under conditions in which extreme tissue oedema occurs both *in vivo* and *in vitro* no extracellular space appears and the swelling is completely confined to certain glial cells.[4,5] It seems inconceivable that the brain should lack an extracellular space, a proposition which would challenge much current thought on the mechanism of nerve conduction as well as accepted views on capillary exchange, but in the present state of knowledge it does not follow that there exists a "blood–brain barrier" for all substances in the shape of an anatomical structure.—I am, etc.,

JOHN DOBBING.

London, S.E.1.

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Respiratory Obstruction in Haemophilic Patients

SIR,—Dr. R. A. L. Leatherdale (April 30, p. 1316), in his article, says that haemostasis "can be achieved only by using animal A.H.G." I would like to mention the following points which may be of interest to readers. The amount of plasma or A.H.G. required depends on the age of the patient. I have used human A.H.G. (equivalent to 600 ml. average normal plasma) pre-operatively and on the first, second, and third post-operative days for the successful performance of a tracheostomy on a severely affected haemophilic boy aged 3 years whose blood contained a high concentration of Bridge anticoagulant.[1]

In Christmas disease, where the same condition is known to occur, it would be useless to use A.H.G., whether of animal or human source. Under cover of fresh blood (or plasma) and stored blood (less than 5 days old) tracheostomy was carried out without incidence on a severely affected boy aged 9 years.

I have seen recurrence of this bleeding in two haemophilic patients. Although in these cases the condition resolved after conservative treatment with fresh blood, this would indicate that careful consideration should be given to the use of animal A.H.G., which is antigenic.

Pre-operative treatment with plasma or A.H.G., whether for teeth extractions of minor or major operations, from my experience is more important than post-operative attempts at controlling the ensuing bleeding. Every effort should therefore be made to give the patient whatever treatment (plasma or A.H.G.) is available *before* embarking on urgent surgery rather than wait for a supply of animal A.H.G.

I am now able to predict the operative bleeding in haemophilia by the following simple method which has been tried in five operations—namely, transplantation of ureter, removal of ectopic vesica, cataract, tonsillec-

tomy, and tracheostomy. A pre-operative sample of the patient's plasma is treated with aluminium hydroxide and incubated *undiluted* with equal volumes of platelet suspension, 1 : 10 normal serum, imidazole buffer *p*H 7.3, and 0.05 M $CaCl_2$. The activity of the plasma thromboplastin formed after 6 minutes is tested by adding 0.1 ml. of the mixture together with 0.1 ml. 0.025 M $CaCl_2$ to 0.1 ml. *patient's* plasma (substrate) at 37° C. The deciding clotting-time of the substrate is 20 seconds; surgery can be proceeded with if the time is below 20 seconds, but it would be inadvisable if a longer clotting-time is observed. In the latter case, a further supply of A.H.G. or fresh plasma would be highly desirable.—I am, etc.,

Blood Transfusion Centre, Brentwood, Essex. F. NOUR-ELDIN.

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Herniae in Africans

SIR,—I have just read, albeit a little late, Dr. E. C. B. Hall-Craggs's paper on sigmoid volvulus in an African population (April 2, p. 1015) and its comparative frequency.

In a series of over 40 consecutive strangulated herniae, all of them oblique inguinal and not one femoral, I encountered 8 herniae en-glissade. They were right-sided and contained caecum and ascending colon and in two cases showed extra lesions (appendicitis and typhoid of lower ileum). This frequency would seem to suggest that there must be some anatomical differences of the large bowel in Africans, allied perhaps to some dietary cause. I wonder if any of your readers have had similar cases and could perhaps suggest a reason for this frequency. I may add that four of the en-glissade herniae occurred in young men.—I am, etc.,

Bibiani, Ghana. MICHAEL ROSEN.

Malabsorption Syndrome

SIR,—Your leader writer (April 30, p. 1340) states that "it is uncertain whether the unfavourable action of gluten is closely connected with the essential lesion in the disease [coeliac disease and idiopathic steatorrhoea]." Such a statement is hardly in accord with the published facts. Not only do the great majority of patients with coeliac disease or idiopathic steatorrhoea show a striking improvement on a gluten-free regimen, with disappearance of all the classical features of the malabsorption syndrome, but it has been clearly proved that many of them display an unequivocal increase of faecal fat to abnormal levels and a return of the features of the malabsorption syndrome if wheat gluten or an appropriate fraction is reintroduced into the diet after a period of remission on a gluten-free regimen.[1 2 3] Indeed, this response to wheat gluten is, in our opinion, an essential step in the diagnosis of gluten-induced enteropathy. Can we doubt that wheat gluten is "closely connected" with the basic aetiology of the malabsorption syndrome in such patients?

It also seems to be assumed by your leader writer that the mucosal damage is the "essential lesion" in this group of patients. What is the evidence for this? Why should the mucosal damage not be a secondary phenomenon?

It is further stated that the mucosal damage is unchanged after treatment on a gluten-free diet. This is not everyone's experience. Some of the reports in the literature on lack of reversal of the mucosal changes on treatment with a gluten-free diet will be found to be based on biopsy studies made in patients who had been on a gluten-free diet but had returned to a gluten-containing diet before the second biopsy was taken. This might invalidate the argument. We have presented clear-cut evidence of striking improvement in the appearance of the small intestinal mucosa in serial biopsies taken from a patient kept on a strict gluten-free regimen.[4] Similar results have been observed in other patients. There is, therefore, no doubt that the histological changes in the mucous membrane in these patients can show improvement on a strict gluten-free regimen. The causes of failure to obtain improvement in some patients require further study.—I am, etc.,

Department of Medical Biochemistry and Pharmacology, The Medical School, Birmingham, 15. A. C. FRAZER.

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Accuracy of the "Breathalyser"

SIR,—My attention has been drawn to the letter by Dr. M. Grace Eggleton published in your journal (April 2, p. 1051) whilst I was in the U.S.A. There are a number of points in her letter which require comment. She is mistaken in supposing that it was largely on a basis of our experiments that the B.M.A. Committee concluded that "a concentration of 50 mg. of alcohol in 100 ml. of blood is the highest that can be accepted as consistent with the safety of other road users." Our results were only part of a considerable body of evidence, both experimental and statistical, considered by this committee. It is unlikely that the committee would have considered relating laboratory results to actual driving situations at all if the laboratory results had not been supported by the field evidence.

Dr. Eggleton is undoubtedly aware of the fact that, in our experiment as in most others, the level of blood alcohol to be related to behaviour change was obtained from direct analysis of blood and not from breath analysis; though our own results and those of many others show that we could have used breath with approximately equal success.

The main point of Dr. Eggleton's letter appears to be to draw attention to the fact that the "breathalyser," in common with all other techniques, has an analytic error. She appears to assume, however, that any discrepancy between blood and breath results is due to inaccuracy in the latter. This is not a justifiable assumption. K. M. Dubowski[1] and T. E. Friedemann and Dubowski[2] draw attention to the different levels of error inherent in different methods of blood analysis. In our experiments, the blood-analysis technique used was that recommended by D. W. Kent-Jones and G. Taylor.[3] For this method, when a known concentration of alcohol in blood is tested, the standard error is 14 mg./100 ml. when tests are made by different analysts, and 6 mg./100 ml. when only one analyst is used. We used one analyst and hence can assume a standard error of 6 mg./100 ml. in our blood values. The standard error of the "breathalyser" against the

obtained blood values was 12 mg./100 ml. When air, bubbled through a known solution of alcohol in water, is tested, the standard error of the breathalyser is smaller, and closely approximates the standard error of the direct blood analysis. Part of the discrepancy noted by Dr. Eggleton is undoubtedly due to error in blood analysis.

The wording of her interpretation of the 95% confidence limits is ambiguous; it is unfortunate that it should have been interpreted by some as meaning that nearly half the cases would show errors as large as 25 mg./100 ml. This is not the case at all. Our distributions[4] show that 62% of all observations differed by less than 10 mg./100 ml., and 80% by less than 15 mg./100 ml., from the figure obtained by analysis of blood. These figures closely parallel those given by other investigators. When E. J. Fennell,[5] for example, used direct blood analysis and the breathalyser in 116 actual traffic cases, he found identical values in 34% of cases, with a discrepancy of not more than 10 mg./100 ml. in 69% and of not more than 20 mg./100 ml. in 97% of the cases. When breathalyser readings differ from the results of direct blood analysis, they tend to be lower rather than higher. In 82% of the discrepancies in Fennell's data, the breathalyser gave the lower figure. None of Fennell's breathalyser figures are higher than the blood values by more than 10 mg./100 ml.; between 2 and 3% are as much as 30 mg./100 ml. lower.

It is widely accepted that the breathalyser can be relied upon not to read higher than the true blood level by more than 10 mg./100 ml., though its error, on the low side, may be slightly greater than this. In the kind of practical situation envisaged by Dr. Eggleton, this is, of course, in favour of the accused. The machine, for reasons which there is not space to elaborate here, tends to give the accused the benefit of the doubt. Discrepancies can be reduced and their extent identified by using H. Ward Smith's[6] technique of analysing duplicate samples and a standard solution with the same ampoule.

Modern methods of breath analysis give results which, for accuracy and reliability, compare favourably with direct blood analysis. They are much quicker and considerably easier to use.—I am, etc.,

G. C. DREW.

Department of Psychology,
University College London,
London, W.C.1.

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Gold that Glisters

SIR,—Dr. Richard Asher's article (April 2, p. 985) was so enjoyable that I hesitate to put him to further expense, but if he is to be consistent should he not give the B.M.A. Library a copy of Thomas Gray's *Ode on a Distant Prospect of Eton College*, that we may be reminded that the gold *glisters* among the dross?—I am, etc.,

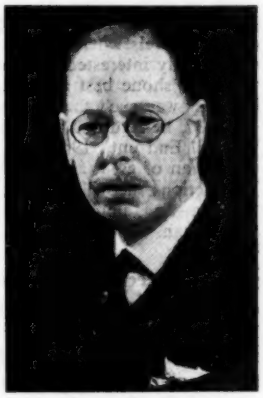
London, W.1 R. CHRISTOPHER HOWARD.

Obituary

C. M. HINDS HOWELL, D.M., F.R.C.P.

Dr. C. M. Hinds Howell, consulting physician to St. Bartholomew's Hospital and to the National Hospital for Nervous Diseases, died on May 9 after a short illness. He was 83 years of age.

Conrad Meredyth Hinds Howell was born on April 26, 1877, the son of a barrister. From Marlborough he went on to Trinity College, Oxford, with an exhibition, and, after taking a first-class in the final honour school of natural science, he gained the senior entrance scholarship to St. Bartholomew's Hospital. Continuing his brilliant academic career, he won the Kirkes and Lawrence scholarships and gold medals and the Brackenbury medical scholarship, qualified in 1902, and graduated B.M., B.Ch. in 1903. As house-physician to Sir Dyce Duckworth he developed an interest in neurology, and after working for a time as demonstrator in the physiology department at Bart's he later held the posts of registrar and pathologist at the National Hospital for Nervous Diseases. These led to his being appointed assistant physician at Queen Square in 1912 and at about the same time he was elected to the staff of the Royal Northern Hospital. He resigned from the latter appointment on becoming an assistant physician at St. Bartholomew's Hospital in 1920. He proceeded M.D. in 1908, and having taken the M.R.C.P. in 1905 he was elected F.R.C.P. in 1910. In later years he served the College as a councillor, censor, senior censor, and as treasurer, and was a representative of the College on the committee of management of the Conjoint Board, being chairman of the committee for four years. He also examined for the London University and for Oxford University.



Dr. Hinds Howell was a popular teacher, and the attendances at his lectures at Bart's were always large. His published work was mostly on neurological subjects, and at the Annual Meeting of the B.M.A. in 1923 he was vice-president of the Section of Neurology and Psychological Medicine. During the first world war he served in the R.A.M.C. and during the second he worked in the Emergency Medical Service. He was also for some years a member of the Central Medical War Committee.

Always a keen sportsman, Hinds Howell played cricket for Marlborough, won the prize cup for rackets, and fenced for Oxford for three consecutive years, winning his matches on each occasion. He was a low-handicap golfer, a good shot, and a keen fisherman. He also found recreation in gardening and philately.

In 1903 he married Dr. Mabel Gulland, who died in 1958. They had three sons, one of whom is a doctor.

J. M. writes: The death of "H.H.," as Dr. C. M. Hinds Howell was commonly known, will be mourned by many, especially by those who had the privilege of working with him and being taught by him. Success throughout his life was his fortunate lot. As a clinical teacher he was superb, with the ability of conveying to the students the essential facts leading to accurate diagnosis, while at the same time not forgetting the finer points in differential diagnosis. But for those who worked for him as house-physician or chief

assistant the charm of his personality was perhaps better appreciated. He was always the same, never upset, and very human in his approach to patients and junior staff, and always understanding. One incident occurred while I was his house-physician which showed his understanding. A patient whose appetite was not good was put on to a bottle of stout twice daily, so on my night round I enjoyed the second. This came to light, and I told "H. H." the story, to which he replied, "Perhaps you were unwise, but I think I should have done the same," and that was the end of the incident.

He was, of course, primarily interested in neurology, but at the same time was an excellent general physician, always willing to learn, and he remarked on one occasion that his house-physicians always taught him something, adding, after a moment, with a twinkle in his eye, "even if it is something not to do." His treatment of trigeminal neuralgia by injection of the ganglion under anaesthesia was a technique which he developed, and at which he was very able, seldom failing to get a complete anaesthesia and a relief of pain. This technique does not seem to have been developed elsewhere, but in his hands it was very effective. Essentially interested in clinical rather than academic medicine, he shone best at the bedside. Indeed, his value as a teacher was such that, although he had retired from Bart's in 1937, he returned again in 1939 in the E.M.S. and taught at Hill End until 1946.

A man of great ability, who taught well and gained many distinctions, he will be greatly missed, for he was a most human and understanding physician, and, above all, a gentleman.

PHILIP ELLMAN, M.D., F.R.C.P.

Dr. Philip Ellman, consulting physician in diseases of the chest to the North-east Metropolitan Regional Hospital Board and physician to the rheumatism unit at St. Stephen's Hospital, Fulham, died on May 10 at the age of 59 after a long and distressing illness, which he bore without complaint.

Philip Ellman began his career as a student in Manchester, taking the Conjoint Diploma in 1923. After holding the post of house-physician at the Mansfield and District Hospital, he went to the West Middlesex Hospital, Isleworth, where he and Mr. Naunton Morgan were registrars together. In 1926 he worked at the sanatorium at Colindale, where he made the acquaintance of the late Dr. Marcus Paterson, for whom he always entertained a high regard and admiration; it was from this friendship that his first interest in chest disease originated. About this time there was some anxiety about his health, and he left England for Switzerland, where he came into close association with Jacquerod, with whom he worked for a considerable time, and with whom he published a joint article on the effect of prolonged rest on the closure of tuberculous cavities in the lung, a subject which excited considerable interest at the time. After working at Lausanne, where he obtained the degree of M.D., he went to study for a time at Frankfurt. He returned to London in 1929, setting up in general practice, though maintaining his interest in diseases of the chest, on which he published his first book, dedicating it to Marcus Paterson. After two or three years of general practice he decided to confine his work to diseases of the chest and to settle in the Harley Street area as a consulting physician. He had taken the Membership of the Royal College of Physicians in 1929, and in 1945 he was elected a Fellow of the College. He soon acquired a considerable reputation as a chest specialist, and later as a specialist also in the rheumatic diseases, in which he had always had a subsidiary interest, having worked for some time with the late Professor Sir Leonard Hill, F.R.S.

Philip Ellman was an enthusiastic and indefatigable worker, and a very good physician. His first consideration was invariably the best interest of his patient, to whom he gave unstintingly of his best, never sparing himself. His clinical judgment was sound, and his methods of examination thorough; and those who consulted him could be certain of receiving sound and practical advice. His mind was always active, and throughout his professional career he kept abreast of the latest developments in scientific medicine. For many years he was responsible for the direction of the chest clinic at East Ham, being consulting physician for diseases of the chest to the North-east Metropolitan Regional Board. He also held a clinic for the treatment of the rheumatic diseases at St. Stephen's Hospital, Fulham Road. During the second world war he was physician in charge of the medical division at the Leatherhead Emergency Hospital, where in collaboration with the staff of King's College Hospital he did his full share of clinical teaching in general medicine.

Ellman contributed extensively to the literature of his profession. In 1952, twenty years after the appearance of his first book on chest disease, he brought out a further and up-to-date volume entitled *Essentials in Diseases of the Chest for Students and Practitioners*, to the value of which and to the comprehensive knowledge of its author a significant testimony was supplied in the foreword written by the late Sir Robert Young. Various other books on the rheumatic diseases, edited by well-known authors, owed no small measure of their importance to Ellman's contributions. In addition to his books he wrote a vast number of articles in most of the well-known medical journals, all clearly expressed and all bearing the imprint of his practical mind. The *British Journal of Diseases of the Chest* (formerly known as the *British Journal of Tuberculosis*) owes an outstanding debt to his editorship, which he continued with characteristic energy and devotion up to within a short time of his untimely death.

Philip Ellman was one of my best and most warm-hearted friends, a high-minded and honourable gentleman, incapable of a mean or ungenerous thought, and a fine example to his professional colleagues of what a good physician should be. Our sincere sympathy is extended to his widow and to his two sons and his daughter.—M. D.

S. T. writes: There will be many among his own colleagues and of like status who would wish to pay their tribute to the life's work of Dr. Philip Ellman, but it is the earnest desire of the general practitioners of East Ham and surrounding districts that they too should be so privileged.

It was 32 years ago that Dr. Philip Ellman attached himself to the county borough of East Ham as a consultant in the field of tuberculosis, and so much of his life's work and research were gleaned by his services among us, for he was indeed a pioneer. He was so rightly proud of the fact that his was one of the earliest, if not the first, clinics in the country to change its name from "tuberculosis dispensary" to "chest clinic," and how much he was justified time has shown to the full. His enthusiasm for radiology was a great feature of his pioneer work. In those early days equipment and facilities were inadequate, and it is a striking example of his efforts when to-day this clinic is acknowledged to be one of the best equipped in the country, and the number of *x*-ray examinations, taking the 1958 figures, has risen to 16,000.

It was, however, his efforts in other directions that so endeared him to the family doctor, for he was indeed a quarter of a century ahead of his time in his offer of open access to the facilities which his clinic afforded, and in his remarkable foresight in seeing the necessity for the family doctor to engage in social medicine. Visiting the clinic, we became his friends—ever welcome. Philip was never too

busy to discuss a case and encouraged us to come again. In the social-medicine sphere he enlisted the aid of a truly remarkable nursing sister, with whom he worked to the end in such perfect harmony. Together they gained the universal confidence and esteem of the G.P.s in and around the neighbourhood, and years ago they had brought the value of this concept of practice to fruition.

Those of us who were privileged to have visited his lovely home at Leatherhead learnt why it was possible for him to have worked so hard and with such enthusiasm. There we met one of the happiest of homes, in which he relaxed in contentment and to the full. To Mrs. Ellman and the family go out our sincerest sympathy, coupled with our gratitude for making his life's work possible.

S. W. PATTERSON, M.D., D.Sc., F.R.C.P.

Dr. S. W. Patterson, formerly senior physician at Ruthin Castle, North Wales, died in London on May 4 after a relatively short illness. He was 78 years of age.

Sydney Wentworth Patterson was an Australian by birth and graduated M.B., B.S. at the University of Melbourne in 1904. For a time he was in general practice in Australia, but before the first world war he came to London and worked under Professor Starling at University College. His inclination at that time was towards research and he was the author of papers on the physiology of the heart and on diabetes. During this time he held a Beit Memorial Fellowship, and in 1916 he took the degree of D.Sc. at the University of London. At the beginning of the first world war he joined the Australian Voluntary Medical Service and went out to France. Later this service was taken over by the R.A.M.C., and at the end of the war he was serving in the rank of major as area pathologist at the base hospital at Rouen. In 1919 he returned to Melbourne as director of the Walter and Eliza Hall Research Institute, but four years later he came back to Britain and was appointed physician at Ruthin Castle, becoming senior physician in 1944. He took the M.R.C.P. in 1926 and was elected a Fellow of the College in 1932.

As a clinician he was specially interested in gastro-enterology, serving as president of the British Society of Gastroenterology in 1954. After the National Health Service came into being he was honorary physician to the Welsh Regional Hospital Board and a member of the Society of Physicians in Wales, of which he was made an honorary member after his retirement to London. A member of the B.M.A. for over fifty years, he was president of the North Wales Branch in 1936–7.

Dr. Patterson married in 1920 Muriel, daughter of Professor Starling. He leaves a widow, four daughters, and one son, who is a consultant plastic surgeon.

P. D. writes: Dr. S. W. Patterson retired from Ruthin Castle only eighteen months ago, and since then, with his usual enthusiasm, had been working in the anatomy department of University College, carrying out research on wound healing. He had a fund of most interesting and instructive stories about general practice as carried out in Australia in his early days. At that time, when patients might be twenty miles away, he would travel to see them on horseback and never knew what he was going to find. He said this experience always helped him to understand the difficulties and interests of general practice, which had its applications even to-day.

His work at Ruthin Castle is well known. He co-operated with Sir Edmund Spriggs in gastroenterological research, particularly on the treatment of peptic ulcers, on diverticulosis and diverticulitis, and on other diseases of the colon and liver.

During his thirty-five years as physician at Ruthin Castle he made a host of friends among patients, doctors, and consultants, and, of course, his own staff. Although slightly reserved on first meeting, he was a most kindly personality and always prepared to give of his utmost in medical knowledge and time to help with patients and relatives. He was most understanding and sympathetic, as I know from personal experience, and his knowledge of medicine was very wide. He wrote many papers, always original, and he also contributed to textbooks, such as *Savill's Clinical Medicine*, *Chamberlain's Medicine*, and the *British Encyclopaedia of Medical Practice*.

It was astonishing to us, his colleagues, how he was able to carry out so much medical work and at the same time follow interesting hobbies—for instance, music, gardening, apiculture, also archaeology associated mainly with the Norman castles in North Wales, and particularly Ruthin Castle itself. For years he had collected data about the Castle and was urged on many occasions to put it into book form, but he always said he would do this in his retirement, but unfortunately, so far as I know, it never materialized.

W. GRANT WAUGH, M.D., F.R.C.S.Ed.

Mr. W. Grant Waugh, for many years a well-known surgeon in Sunderland, Co. Durham, died at Drayton Valley, Alberta, Canada, on April 25. He was 73 years of age.

William Grant Waugh was born in Edinburgh and educated at George Watson's College. He graduated M.A. in 1905 and studied law before becoming a medical student at Edinburgh University. Graduating M.B., Ch.B. in 1910, he proceeded M.D. in 1913 and was elected a Fellow of the Royal College of Surgeons of Edinburgh in 1924. He settled in Sunderland in 1910 and for some years was in general practice, but this he ultimately gave up to devote himself to surgery. During the first world war he served with the R.A.M.C., attaining the rank of colonel. He was officer-in-charge of the surgical division of the 4th General Hospital.

Returning to Sunderland, he was appointed assistant surgeon to the Children's Hospital in 1922 and to the Royal Infirmary in 1924, and consulting surgeon to the latter in 1946. Besides being on the staff of the Monkwearmouth and Southwick Hospital, Sunderland, he later became orthopaedic surgeon to the Darlington Memorial Hospital and to the Sedgefield General Hospital. He was a past-chairman of the Sunderland Division of the B.M.A. and president of the Northern Counties Medical Society in 1939. Two years ago he suffered from a severe illness, but with his characteristic courage and pertinacity he weathered the storm, although it did leave its mark upon him. Eighteen months ago he left Sunderland to live with his son, Dr. Ian Grant Waugh, firstly at Mercoal and latterly at Drayton Valley, Alberta, where his services were utilized by the local hospital and where he continued to work until within a few days of his death.

Dr. A. A. McINTOSH NICOL writes: Mr. Grant Waugh's legal training gave him that inquiring mind which showed itself so often and with such conspicuous success in his approach to his investigations and research, and these commenced while he was still a general practitioner. He invented numerous gadgets in orthopaedics and described an original plastic repair operation on a popliteal aneurysm, but it was for his work on the treatment of the arthritic joint by lactic acid that he became known both nationally and internationally. He travelled extensively both on the Continent and in America and Canada to give lectures on this treatment and was honoured by being asked to lecture to the French Academy of Medicine in 1949. Criticism there may have been by some for this particular therapy, but those who were closely associated with him and saw his results could never doubt the relief his method of treatment gave to thousands of sufferers whose gratitude was unbounded, and these investigations were carried out while he was still a busy general surgeon, although pressure of work made him ultimately devote his time to orthopaedics. He carried on also an extensive practice in Harley Street in addition to his work in Sunderland and in Co. Durham. In spite of all his commitments he never appeared hurried or flurried and for ever retained his placid demeanour,

always finding time for a talk about his particular work and medicine generally, always with a quip and always with a charming smile.

He wrote extensively in the medical press, and when the occasion arose he would give vent to his feelings in the lay press on non-medical subjects if necessary, and particularly when he felt that some vital principle had been violated, in beautifully well-chosen words.

Bill, as he was known to his friends, was a doughty fighter, which his opponents would soon realize, and he would not spare them when the occasion arose. He did not suffer fools gladly, but fundamentally he was soft-spoken, kindly, and courteous—a true gentleman—always ready to help, and those who knew him well could never have found a more loyal friend. He had his sorrows and disappointments in life and he suffered a great blow on the death of his younger son while on active service in Italy a few days before the Armistice, but all these he bore with a dignity and fortitude one admired. He was widely read, and his knowledge of the classics and modern literature could have been bettered by few medical men. He loved life and got great pleasure from horse-racing (at one time he was surgeon to the Catterick racecourse), from his fishing expeditions to Scotland, from deer-stalking, and from visits to a Scottish–English international Rugby match. Perhaps he derived most pleasure from entertaining his friends in his own home. He was a wonderful host, always warm-hearted and charming, and a real connoisseur of wines. He retained his youthful figure and remained a gay spirit—and such men as Bill Waugh are never easily replaced. He belonged to an older generation, but had the facility of never growing old mentally.

He is survived by his wife, formerly Miss Enid A. Pickersgill, a well-known Durham County tennis and golf player, and by his son, Dr. Ian Grant Waugh, and to them we extend our deep sympathy.

One feels he died as he would have wished, in harness to the end, and feeling he had been a burden to no one. For Bill Waugh perhaps the lines by Stevenson are appropriate:

> "Glad did I live and gladly die
> And I laid me down with a will."

Sir SYDNEY SMITH writes: Mr. Grant Waugh will be missed and mourned by a large circle of colleagues and friends, for he had a great capacity for making friends, was a good all-round sportsman, and a charming companion.

Sir DONALD McGAVIN, C.M.G., D.S.O., M.D.
F.R.C.S., F.R.A.C.S., F.A.C.S.

Sir Donald McGavin, formerly Director-General of Medical Services, New Zealand, and consulting surgeon to Wellington Hospital, died suddenly at his home in Wellington on May 7.

Donald Johnstone McGavin was born on August 19, 1876, and educated at King Edward's High School, Birmingham, Mason University College, Birmingham, and at the London Hospital. Qualifying in 1899, he graduated M.B. in 1900, and proceeded M.D. in the following year, winning a scholarship and the gold medal in medicine and in obstetric medicine. He went out to New Zealand after serving as a civil surgeon in the South African war, and then returned to London to take the F.R.C.S. in 1904. His appointment as surgeon to the Wellington Hospital followed soon afterwards.

During the first world war he served with great distinction and remained in the Army for several years thereafter. For more than half a century he was an outstanding figure in the New Zealand medical profession, being senior surgeon at Wellington Hospital, a Foundation Fellow of the Royal Australasian College of Surgeons, and a former president of the New Zealand Branch of the B.M.A.

We are indebted to Sir GORDON GORDON-TAYLOR for the following appreciation: The death of Sir Donald McGavin within a very few months of his 84th birthday has brought to a close the life of a well-known New Zealand surgeon and an ever-popular citizen of New Zealand's capital. After a distinguished undergraduate career at Birmingham, he worked at the London Hospital in the great days of Sherren and Rigby, Harold Barnard, Arthur Keith, and Leonard Hill, securing his F.R.C.S. in 1904. New Zealand beckoned invitingly to a number of well-qualified young men at that period—such as David Storer Wylie, James S. Elliott, Carrick Robertson, and William Percy Gowland, who taught anatomy to generations of Otago students—and McGavin became surgeon to the Wellington Hospital. During the first world war he served in Egypt and Salonika, and then distinguished himself as A.D.M.S. to the New Zealand Division, being mentioned in dispatches four times, and awarded the D.S.O. after the Battle of Messines, where the New Zealand Division was intercalated between the famous 36th Ulster Division on its left and the 3rd Australian Division on its right. It was at Balleul on this occasion that I first met McGavin. Towards the end of the war he was with his New Zealanders when they took the walled town of Le Quesnoy by escalade, mounting on ladders upon its ancient ramparts. The C.M.G. came to him at the close of hostilities. From 1919 to 1924 he was Director-General of the Medical Services of New Zealand, and in 1921 he was knighted. He was made a major-general in 1923.

His popularity and his administrative ability brought him many public burdens to assume: in the later period of his life he became a director and ultimately chairman of directors of the well-known New Zealand newspaper the *Dominion Mail*.

In the thirties of this century the only approach for examiners for the Primary Fellowship in Dunedin was across the inhospitable Tasman Sea in the old *Monowai*, but at the end of the sea journey there was the delightful Wellington Club, with hosts like McGavin, Duncan Stout, Bruce Rennie, and others: this was indeed a haven on the way to the South Island. My colleague-examiner in 1934 was George Buckmaster, who had previously visited New Zealand in a similar capacity and who had been tremendously impressed by McGavin's personality on that occasion. Both men retained their zest for living: both loved "laughter and the love of friends." The very mention of the Wellington Club, where I stayed on not a few occasions, will always bring to my mind the name of Donald McGavin, a gallant soldier and a firm and delightful friend. His last few years were saddened by the loss of his charming wife, but even in his eighty-fourth year he was on the eve of departing for Britain when death suddenly came to him. His son, Donald, is one of the surgeons to the Leicester Royal Infirmary.

Medical Notes in Parliament

ROYAL COLLEGE OF PHYSICIANS UNDER FIRE

[FROM OUR PARLIAMENTARY CORRESPONDENT]

The Royal College of Physicians of London Bill was given its second reading by the House of Commons on May 9, after Dr. BARNET STROSS (Stoke-on-Trent, Central, Lab.) and one or two others had used the opportunity presented by the appearance of the Bill to express some discontents about the College that had been raised with them. The principal objects of the Bill have already been recorded in this column (April 23, p. 1285), and no objection is taken to them from any source. The grievances have also been outlined—the method of electing Fellows—by Fellows only, and in person, with no postal vote; and that only two representatives of the Members have seats on the governing council.

Fear of Unpopularity

One of the comments made by Dr. STROSS in elaborating these points was that Members of the College had told him that in their view merit awards more easily followed

when Fellowship was attained; therefore they felt nervous of criticizing the constitution of the College or the method of election for fear that they might become unpopular. That might be wrong on their part, he said, but he was voicing views that had been put to him. He was told also that although the two elected representatives of the Members on the council could propose an alteration in the by-laws for election to Fellowship they had never done so. Neither had any Member of the College ever complained to the College. He found it rather frightening that representations had been made to him and his supporters as M.P.s, and that officers of the College should have no knowledge that there was any feeling in the matter. The dissatisfaction had apparently not reached the upper circles of the College itself. The Members felt that they were disfranchised. Dr. Stross was asked how many Members had written to him on this subject, and replied that he had received eight letters. One of them, which he read, stated:

"In company with very many other physicians who are Members of the College I feel that the conduct of the College's affairs is such that we are, as I think you have said, disfranchised. The conduct of the College's affairs seems archaic and contrasts very badly with the other professional bodies of similar standing."

"B.M.J." Leader Recalled

He quoted also a paragraph from a leading article in the *British Medical Journal* of April 7, 1956, entitled "The Gold-headed Cane":

"Those who have a great affection for something that has had a local habitation and a name in the world of medicine since 1518 should not feel guilty of impiety in voicing criticisms that are widely if obscurely felt. The antique mask the College wears on its official occasions has a certain faded charm of its own, but it sorts only too well with its present confusion of purpose. The Royal College of Physicians of London is faced with a challenge or a series of challenges with which it has so far come into only most reluctant and hesitating contact. Upon its ultimate response its welfare depends, and much of what is at the heart of medicine."

Sir WAVELL WAKEFIELD, a Conservative and the M.P. for St. Marylebone, told the House that he had received many letters from constituents asking him to support the Bill and expressing anxiety lest it might be rejected. In none of them had there been a single complaint such as Dr. Stross had raised. That did not mean such grievances did not exist. He commended Dr. Stross for taking the opportunity to ventilate those grievances, and expressed the hope that they would be seriously considered by those responsible for the running of the College. Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) widened the discussion somewhat by first of all including Fellows among those who had said to him that it was good that the structure and constitution of the College should come under review by the House, and secondly by reiterating a complaint he has voiced before that the teaching of medical students had fallen far behind the needs of the time, and that they were taught next to nothing of psychological medicine. He hoped that before long there would be a royal college of psychiatry.

Fallacy of the Postal Vote

Sir MALCOLM STODDART-SCOTT, another of the medical M.P.s and Conservative member for Ripon, spoke up for the Royal College, "an admirable and ancient institution" which had created a standard of medicine that had produced some of the finest physicians in the world. The House should make certain before suggesting changes that they would be for the better. To have a postal vote among 4,000 Members would not ensure academic distinction for those most worthy to receive it. The best way to get the right awards was to have the selection by the smallest number possible, not the largest. Dr. Stross had expressed the dissident views of eight members. Among 4,000 there would always be some dissatisfied.

Dr. DICKSON MABON (Greenock, Lab.) said that that argument would mean a special committee of the Fellows to decide who should be new Fellows, and the remainder of the 900 Fellows would have no part in the election. About 12 Members had spoken to him about the College, and he had had six letters. All except one had asked him not to read the letter or mention the name. It smacked very much of an oligarchy dispensing patronage; one must not offend it, or one might not get even a reasonable share of the patronage. There was something fundamentally wrong when medical men should be unable because of fear of their incomes and prospects to speak up and make radical constitutional changes within their own organization. He had expressed opposition on behalf of some who had taught him as a student, on behalf of men senior to him, on behalf of men who were at the university with him. A change in the government of the Royal College was sadly needed.

Delaying Amendment Withdrawn

None of the speeches was critical of the objects of the Bill. Miss EDITH PITT, Parliamentary Secretary to the Ministry of Health, made the point that there was agreement that these were admirable, and that the issues which had been raised were outside the Bill's province. Dr. STROSS withdrew his motion to delay the Bill's second reading for six months in the hope that the Royal College would study what had been said, and the Bill was read a second time.

Pharmaceutical Operational Research

Lord Cohen of Birkenhead is to be chairman of a standing committee appointed by the Central Health Services Council at the suggestion of the Minister of Health to advise on operational research in the pharmaceutical services. This was announced by Mr. D. WALKER-SMITH on May 16, when he stated that the full terms of reference to the standing committee were:

"Having regard to the need to avoid unnecessary expenditure in the pharmaceutical services provided under Part IV of the National Health Service Act, 1946, to advise the Minister on (1) the operational research which should be undertaken in relation to those services, involving the collection of statistical, economic, and socio-medical data, and on (2) the interpretation of such data."

The members are: Mr. E. F. Collingwood, Sir Hugh Linstead, M.P., Dr. A. Talbot Rogers, Mr. J. C. Hanbury, Mr. H. Noble, Dr. H. C. Faulkner, Dr. J. C. H. Bird, Dr. B. Abel-Smith, Mr. L. C. H. Tippett, Mr. R. Falk, Mr. M. Perrin, and Mr. G. McLachlan.

Medico-Legal

HOW TO DECLARE A MAN ALIVE

[FROM OUR LEGAL CORRESPONDENT]

Coroners' courts, like other judicial bodies, sometimes make mistakes, but the means of rectifying such mistakes are not always straightforward, and certainly not generally well known. The South Gloucestershire coroner held an inquest on March 3 at Dursley on a body found on a railway line. Relying on evidence of identification given by a police constable, the coroner recorded the death of one Tom Williams, aged 60, a tramp. However, Tom Williams reappeared, alive, at Easter (*Daily Telegraph*, April 23).

If an inquest has been properly held, with a view of the body, the coroner is *functus officio* and cannot reopen it. A new inquest can be held without preliminary legal steps only if the first inquest was so irregular as not to amount to an inquest at all. This would be the case, for instance, if the inquest had been held without a view of the body, or if, as occurred in one case, the coroner at the view was shown the wrong body.[1] Otherwise a new inquest can be held on a body only if the first inquest is quashed by the High Court.

High Court's Statutory Powers

The High Court has certain common law powers to quash an inquest for irregularity. The Court also has

statutory powers under the Coroners Act, 1887, Section 6, to quash an inquest on a number of stated grounds. More recently the Coroners (Amendment) Act, 1926, Section 19, made it clear that these powers could be exercised in any case where the Court is satisfied that by reason of the discovery of new facts or evidence it is necessary, or desirable, in the interests of justice that an inquest on a death should be quashed, and that another should be held. The Court can only exercise these statutory powers upon an application by, or under the authority of, the Attorney-General. Application is usually made by an interested party, but the coroner himself may apply if he becomes dissatisfied with his verdict.

This procedure is cumbersome, and a simpler method is available. A coroner may hold an inquiry for the purpose of making a certificate upon which the registrar of deaths may correct his register. Under Section 29(4) of the Births and Deaths Registration Act, 1953, where an error of fact or substance (other than an error relating to the cause of death) occurs in the information given by a coroner's certificate concerning a dead body upon which (or a death touching which) he has held an inquest, the coroner, if satisfied by evidence on oath or statutory declaration of the existence of the error, may certify to the registrar the nature of the error and the true facts of the case. Upon that certificate, the registrar may correct the error in the register by entering in the margin (without any alteration of the original entry) the facts as certified by the coroner. This was the course adopted by the South Gloucestershire coroner on April 22. After taking evidence from Tom Williams and from the police constable who had given evidence at the original inquest, the coroner expressed himself as satisfied that a genuine mistake had been made.

Section 29(4) Permissive Only

It is important to notice that the provisions of Section 29(4) of the 1953 Act are permissive only. The coroner *may* make an inquiry under this Section, but he cannot be compelled to do so by an order of *mandamus*. Moreover, if the coroner does make an inquiry and make a certificate to the registrar, the registrar *may* correct the error in the register, but he cannot be compelled to do so. If either the coroner refuses to make an inquiry or the registrar to act on the certificate, the only method of redress open to some interested person would be by application to the High Court. An order of the High Court might also be required in some other cases as where, for instance, a person is charged by a coroner's inquisition with murder, manslaughter, or infanticide as a result of an error of this sort.

ASTRAL CONCEPTION REJECTED

[FROM OUR LEGAL CORRESPONDENT]

In the Divorce Court on April 6, Mr. Justice Hewson rejected the submission that a wife's baby had been supernaturally conceived (*Yorkshire Post*, April 7). In doing so he presumably took judicial notice of the normal course of nature (as he was entitled to do), and found the wife's evidence insufficient to displace the view so formed.

Mr. Albert Edward Bull, of Stepney, was granted a decree *nisi* on the grounds of the adultery of his wife with a married coloured man who had been studying to be received into a minor grade of a Christian order of friars. The wife met the co-respondent when she was canvassing for the Jehovah's Witnesses in 1956, and their religious discussions thereafter bound them together. In the same year marital relations between Mr. Bull and his wife ceased, but in May, 1958, the wife gave birth to a son. The co-respondent did not appear, but the wife denied adultery, alleging that the child was conceived between the astral bodies of herself and the co-respondent eleven years before they met in the flesh, on about V.J. Day, in 1945. After hearing evidence of inclination to adultery and of the registration of birth showing the co-respondent as father, and taking into consideration the fact that the child appeared to have some coloured blood, the judge found adultery proved and ordered the co-respondent to pay £200 damages.

[1] Jervis, J., *On the Office and Duties of Coroners*, 1957, p. 185, Sweet and Maxwell, London.

CORONERS' CASES

Barbiturates and Alcohol

A voluntary patient at the Pastures Hospital, Mickleover, died on April 2 as a result of the "deadly combination" of barbiturates and alcohol. He was a man of 47 who was undergoing treatment for chronic alcoholism. The medical superintendent, Dr. E. U. H. Pentreath, told the coroner that he was one of a group of patients who were responding well to treatment. He was allowed outside the hospital in the evenings and there was no reason to suppose he went drinking on these occasions. A student male nurse, aged 19, said in evidence that he gave the deceased a routine dose of 6 gr. (0.4 g.) of sodium amytal on his return to the dormitory. Dr. I. Mackenzie, the pathologist, said in evidence that alcohol and barbiturates were a very deadly combination and could cause death very quickly.

Recording a verdict of death by misadventure, the Derby county borough coroner, Mr. R. J. H. Cleaver, expressed his concern that steps should be taken to ensure that barbiturates are not given to patients who might have been drinking (*Yorkshire Post*, April 4).

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on April 28 the following degrees were conferred:

D.M.—A. Ryle, *F. I. Caird.
M.Ch.—*R. T. Campbell.
B.M.—D. G. Sargant.

*In absence.

UNIVERSITY OF GLASGOW

Dr. Alexander C. Forrester has been appointed Reader in Anaesthetics and Dr. Henry E. Hutchison, Reader in Haematology.

UNIVERSITY OF DUBLIN

SCHOOL OF PHYSIC, TRINITY COLLEGE

The following candidates have been approved at the examination indicated:

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—*Part II:* J. McHugh, M. White.

UNIVERSITY OF LONDON

On March 30 the degree of M.D. was awarded by the Senate to P. T. Flue, D. F. N. Harrison, and R. J. Shephard.

The degree of Ph.D. in the Faculty of Medicine was awarded in March by the Vice-Chancellor on behalf of the Senate to K. L. Cotton (Postgraduate Medical School of London), E. J. K. Penikett, M.B., B.S. (Guy's Hospital Medical School), M. Rafiq (School of Pharmacy), Joan Vernikos (Royal Free Hospital School of Medicine), and A. Das (Chelsea College of Science and Technology).

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At a quarterly comitia of the College held on April 28, with the President, Sir Robert Platt, Bt., in the chair, the following were elected Fellows of the College:

W. S. Whimster, M.D. (Nottingham), J. C. J. McEntee, M.D. (London), L. G. Norman, M.D. (London), W. A. Hawk, M.D. (Canada), P. W. Hutton, M.D. (Uganda), R. J. Vakil, M.D. (India), B. McArdle, M.D. (London), Lord Taylor of Harlow, M.D. (London), N. F. Coghill, M.B. (London), M. Sarwar, M.B. (Pakistan), R. Mowbray, M.D. (Durham), E. B. French, M.B. (Edinburgh), Sir Stanford Cade, F.R.C.S., F.R.C.O.G. (London), A. A. G. Lewis, M.D. (London), T. Parkinson, M.D. (Harpenden), A. Jordan, M.B. (Sheffield), W. L. Llewellyn Rees, M.D. (London), R. B. Thompson, M.D. (Newcastle upon Tyne), M. E. MacGregor, M.D. (Warwick), D. A. R. Pond, M.D. (London), W. E. Henley, D.M. (New Zealand), B. D. R. Wilson, M.B. (London), A. N. T. Meneces, M.D. (Chester), C. W. M. Whitty, D.M. (Oxford), R. R. H. Lovell, M.D. (Australia), L. Eales, M.D. (South Africa), C. H. Edwards, M.R.C.P. (London), J. M. Jefferson, D.M. (Birmingham), P. F. Borrie, M.D. (London), J. L. Frew, M.D. (Australia), J. P. Shillingford, M.D. (London), H. L. Ellis, M.D. (Oxford), J. D. S. Cameron, M.D. (Edinburgh), A. E. Mourant, D.M. (London), H. Scarborough, M.B. (Cardiff), D. F. Cappell,

M.D. (Glasgow), R. G. Macfarlane, M.D., F.R.S. (Oxford), Sir Clement Price Thomas, M.D., F.R.C.S. (London), A. Wallgren, M.D. (Stockholm).

The following, having satisfied the Censors' Board, were elected Members of the College:

June P. Arnold, M.D., B. Ashworth, M.B., B. W. D. Badley, M.B., M. Barry, M.B., M. Brown, M.B., Major, R.A.M.C., A. A. Buchanan, M.B., D. N. Chanmugam, M.B., R. D. Cohen, M.B., J. S. Comaish, M.B., J. Connolly, M.B., G. H Cooray, M.D., A. H. Dimond, M.B., Captain, R.A.M.C., C. G. B. Downie, M.B., Major, R.A.M.C., A. K. Dutta, M.B., A. T. T. Forrester, M.B., L. Fry, M.B., M. B. Ghosh, M.B., B. K. Gupta, M.B., H. M. Hodkinson, B.M., E. E. Jones, M.B., A. S. R. Kambawi, M.D., H. J. Liebeschuetz, B.M., D. R. London, B.M., J. N. MacCaig, M.B., A. G. Malleson, M.B., Valerie J. Marrian, M.B., P. D. Marsden, M.B., N. M. C. Mayne, M.B., G. A. H. Miller, B.M., M. G. Miller, M.B., R. O. Moore, M.B., P. M. J. O'Brien, M.B., A. T. Otaki, M.B., M. S. N. Pathy, L.R.C.P., O. H. D. Portsmouth, M.B., A. I. Rae, M.B., G. Ross, M.B., L. Stimmler, M.B., F. Stratton, M.D., M. Visuvaratnam, M.B., J. G. Walker, M.B., J. M. Walker, M.B., R. E. O. Williams, M.D., P. K. Wong, M.B., E. G. Wooster, M.B.

Licences to practise were conferred upon the following 178 candidates who have passed the final examination in medicine, surgery, and midwifery of the Conjoint Board, and who have complied with the by-laws of the College:

M. F. A'Brook, A. P. Adams, E. J. J. Almeida, J. J. R. Almeyda, Elisabeth M. Appleby, Jean Arnold, K. Arthur, N. H. Atkinson, R. Balcon, M. A. Barnett, J. Barrett, J. M. Barry, Ann A. Barton, A. S. Batainch, B. Batten, Pauline J. Begley, H. E. Berry, Delia A. M. Bickerton, J. Bienenstock, Jean M. Bird, R. C. Bland, G. Blandford, Barbara M. Bonner-Morgan, P. N. Booth, W. J. Boyle, F. E. Bruckner, Jill A. Bullimore, M. J. Campbell, P. C. Cann, D. McD. Cardwell, A. A. Carrasco, J. A. Carter, P. G. Cassell, D. N. Challacombe, H. M. Clink, C. L. Colton, A. R. Cook, D. E. Cooksley, Dorothy J. Cooper, T. B. Cork, Sheila A. Corrin, Helena M. J. Cotter, J. E. Crockett, J. C. Cummins, M. F. Cuthbert, D. J. W. Darby, R. N. Davies, Jill Dean, P. B. Deverall, Sybil B. Diggle, Ewa M. Dragowska, B. R. Duncan, E. C. Emelife, A. W. G. English, J. D. Eustace, C. E. Evans, P. O. Fasan, R. E. Faulkner, I. T. Field, H. M. Fisher, T. R. Fisher, D. M. Flanagan, Sally E. Flew, K. G. E. Frohnsdorff, Janet K. Gambell, D. H. Georgelin, B .E. Gilliver, Sharron H. Gilmour, J. C. Gingell, P. L. Girolami, A. Gletsu, R. A. Goldfinch, R. J. Green, Susan R. Greenwood, R. N. Gruneberg, A. D. G. Gunn, Pamela M. Haigh, T. R. Hailstone, J. E. Hale, J. M. Hawkings, Alethea B. Heal, J. Herbert, Rosemary E. Heron, R. D. Hill, B. L. Houghton, R. H. Hughes, G. A. Hunter, I. M. James, M. L. James, Cecily A. Jenkins, B. D. Jones, H. H. G. Jones, H. D. Kaufman, M. J. Kestle, Edvina M. King, Thilla Krikler, D. A. H. Langman, A. Levine, D. J. Lightman, M. J. Lipton, J. S. P. Lumley, L. Lupin, Leonie M. McEwen, M. T. MacMahon, I. F. Macrae, D. J. Martin, M. H. J. Martin, R. C. Martin, C. A. S. Mason, J. R. Massy, C. D. Matthews, L. S. Mehta, G. M. Michael, B. S. Michaels, J. S. Musgrove, Daphne M. Newman, May Ning, E. R. Norton, V. B. Odunlami, M. J. Olver, J. D. Parry, Catherine S. Peckham, M. J. Pemberton, J. P. Pettavel, Sally J. Phillips, Dianne E. Philp, J. Pilcher, C. J. F. Pool, D. Prothero, A. R. Reece, G. M. Rees, G. Reiman, D. S. Restall, Christine E. Riley, I. E. W. Robertson, R. E. Robinson, N. C. Roles, Wendy Roles, J. B. Sales, N. A. Samaan, Elizabeth Shindler, A. J. Simmonds, G. W. Simonds, D. H. Smith, Joanna South, P. E. Spicer, Charmian R. L. Stephens, Patricia S. Stephenson, Anne K. Stewart, K. E. Tanner, W. H. Thomas, Ada A. Thornton, C. J. Todes, D. A. Toms, L. N. Travis, K. Ll. K. Trick, Irene J. Tufft, W. Ursell, J. A. S. Vick, H. Wagman, A. E. Walker, D. E. Walter, M. M. Watkins, W. N. D. Watson, J. L. Wearn, P. C. Weaver, C. L. W. Webb, P. Wentworth, B. W. Whalley, N. R. Whiting, J. N. Whittaker, A. R. F. Williams, Wendy E. Williams, R. A. Wiseman, Bridget M. Wood, R. B. Woodd-Walker, M. W. G. Wren, C. H. Young.

Diplomas in Medical Radiodiagnosis, in Medical Radiotherapy, in Anaesthetics, in Child Health, in Physical Medicine, in Psychological Medicine, and in Industrial Health were granted, jointly with the Royal College of Surgeons of England, to the successful candidates whose names were printed in the report of the meeting of the Royal College of Surgeons of England in the *Journal* of May 7 (p. 1438).

Diplomas in Laryngology and Otology were granted, jointly with the Royal College of Surgeons of England, to M. W. Brown and Maung Maung Myint.

Diplomas in Ophthalmology were granted, jointly with the Royal College of Surgeons of England, to P. W. E. Downes and to the other successful candidates whose names were printed in the report of the meeting of the Royal College of Surgeons of England in the *Journal* of May 7 (p. 1438).

Diplomas in Tropical Medicine and Hygiene were granted, jointly with the Royal College of Surgeons of England, to J. Olafsson and to the other successful candidates whose names were printed in the report of the meeting of the Royal College of Surgeons of England in the *Journal* of May 7 (p. 1438).

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At a quarterly meeting of the College held on May 3, with the President, Dr. A. Rae Gilchrist, in the chair, the following were elected Members of the College:

E. McC. McGirr, R. N. Johnston, D. S. Smith, B. A. Ranga Rao, R. Lamb, N. E. Loos, F. D. Honneyman, E. A. M. Wood, T. C. Nicol, A. Ramasubramanian, J. K. Davidson, B. H. Khan, N. S. Dixit, J. N. Mishra, M. A. Jafri, Sheila M. Pereira, J. S. Madden, I. W. Pinkerton, Isabella C. Ferguson, W. G. Wenley, B. Ashworth, Pamela M. Lambden, R. Shulman, P. K. Wong, R. G. Sourjah, G. J. Addis, K. S. Van Eeden, B. Cooper, P. D. Moylan, K. C. Patel, P. A. Barker, S. Ranjan, S. K. Vohra, J. Johnson, G. C. Pandey, J. H. P. Willis, O. P. Thaman, I. H. Jones, J. N. G. Davidson, B. S. L. Kidd, B. R. Knowles, G. T. D. P. Pillai, B. M. Goswami, P. McDonald, A. Pringle, Enid J. Cartwright, Aung-Than-Batu, G. O. Onuaguluchi, A. Nagaraj, S. Kumar, B. Mittra, A. E. Charaoui.

Vital Statistics

Road Deaths in March

Accidents on the roads of Great Britain during March caused the deaths of 493 people—78 more than in March, 1959. The total of killed and injured was 23,575, a slightly smaller figure than last year. About half the pedestrians killed (197) were over 60, and about a quarter were children. In the first quarter of the year pedestrian fatalities increased by 26%. Police reports show that 514 learner drivers were involved in fatal or serious accidents in March—125 more than in February—and in this figure were included 424 drivers of two-wheeled vehicles.

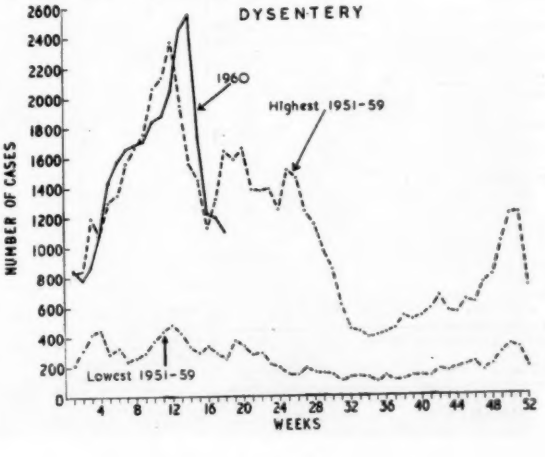
Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

Dysentery	Week Ending	
Lancashire	227	196
Liverpool C.B.	38	30
Oldham C.B.	13	13
Preston C.B.	9	16
Morecambe and Heysham M.B. ...	6	21
Worsley U.D.	13	16
London	162	144
Battersea	1	11
Bermondsey	9	12
Hackney	10	14
Islington	32	19
Lambeth	9	10
Lewisham	15	10
Southwark	15	12
Wandsworth	6	16
Middlesex	63	74
Ealing M.B.	9	15
Enfield M.B.	3	11
Norfolk	60	50
Norwich C.B.	17	34
Glasgow	124	126
Angus County	2	110

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.



INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 30** (No. 17) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	3	1	1	0	2	3	1	2	0	1
Dysentery ..	1,199	162	262	16	12	996	87	208	7	2
Encephalitis, acute	3	0	0	0		1	0		0	
Enteric fever:										
Typhoid ..	2	1	0	0		2	0	0	1	
Paratyphoid ..	4	0	0	0		2	1	0	0	
Food-poisoning ..	137	13	8	1		257	72	14	0	
Infective enteritis or diarrhoea under 2 years				6	33				6	18
Measles*	2,273	112	38	12	31	14,317	675	636	468	156
Meningococcal infection	20	1	12	0		22	4	10	0	5
Ophthalmia neonatorum	16	1	7	0		30	2	3	0	
Pneumonia† ..	342	15	224	8	6	320	21	175	10	10
Poliomyelitis, acute:										
Paralytic ..	4	0	0	} 0	0	{ 16	2	0	} 0	
Non-paralytic ..	1	0	0			4	2	1		
Puerperal fever§ ..	169	23	11	1		212	32	8	2	
Scarlet fever ..	520	32	45	25	15	919	64	64	26	21
Tuberculosis:										
Respiratory ..	458	48	68	11		630	57	97	16	
Non-respiratory	70	5	6	9		69	9	17	1	
Whooping-cough	994	67	185	10	44	870	34	68	39	104

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	12	1	1	0	0	4	0	1	0	1
Influenza	35	0	1	0	1	37	2	0	0	3
Measles		0	0	0	0		1	0	0	
Meningococcal infection		0	0				0	1		
Pneumonia ..	607	41	26	16	4	416	37	20	10	12
Poliomyelitis, acute	5	0		0	1	0	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 79	{ 5	10	0	1	} 73	{ 4	4	1	1
Non-respiratory		0	0	0	1		1	1	0	0
Whooping-cough	1	0	0	0	0	0	0	0	1	0
Deaths 0–1 year ..	347	29	39	9	6	289	38	21	7	12
Deaths (excluding stillbirths) ..	10,154	801	636	139	161	9,285	759	528	133	166
LIVE BIRTHS ..	15,994	1259	1150	342	473	14,724	1234	1034	277	406
STILLBIRTHS ..	342	20	19			342	31	17		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Colour Television at R.C.S.

The history of cancer research might be described as conditioned by the history of microscopy, said Professor A. HADDOW, F.R.S., introducing a closed-circuit colour television lecture and demonstration on cancer research at the Royal College of Surgeons on May 10. Ciba's novel Eidophor—the image-bearer—system of colour television was appropriately used, since it enables the field of the microscope to be projected on to large-size screens. With its aid, cell, chromosome, and virus microscopy in cancer research was illustrated and discussed in a three-part programme by Professor G. J. CUNNINGHAM, Professor P. C. KOLLER, and Dr. R. J. C. HARRIS, helped by their collaborators.

Medical Recording Service

The College of General Practitioners' Medical Recording Service—its work was described in the *Journal*, September 6, 1958, p. 583—has recently completed two new items: one, "The College of General Practitioners, 1953–1959," is the first of a series which will record landmarks in the College's development. This lasts for 30 minutes and is on tape or L.P. disc. The second is a symposium on "Difficulties in General Practice," in which three general practitioners from different parts of Britain and three from New Zealand have recorded 10-minute talks on some of the difficulties with which they are faced. This is on tape only, and runs for about 60 minutes. Recordings, which are loaned free, are normally available only to members and associates of the College, though there are some exceptions to this rule, and inquiries should be addressed to the College's Medical Recording Service at 41, Cadogan Gardens, London, S.W.3.

Hospital Architects

The demand for more architects in the highly specialized field of hospital architecture is rising sharply, and the Ministry of Health is stimulating recruiting to the design staffs of the 15 Regional Hospital Boards in England and Wales by the following measures:

New salary scales will come into effect on July 1; the special post of Assistant Regional Architect may be sanctioned for major schemes of about £1m.; the Ministry has strengthened its own architectural division during the past year. To familiarize architects with the basic principles of hospital design special courses have been planned: one—for those without hospital experience—at the Royal Institute of British Architects from July 11 to 15, supported by a Ministry of Health hospital design exhibition in the R.I.B.A. Galleries from July 7; the other—a more detailed residential course at Oxford from August 22 to September 15—will deal with many special aspects of hospital planning such as the prevention of cross-infection. It is expected that £31m. will be spent on hospital building in 1961–2. The figure in 1955 was around £10m.

Graduate Nurses

A scheme of training in which students will be expected to graduate in arts or science before a final qualification in nursing is being started in Edinburgh in the autumn. In announcing the course, the first of its kind in Great Britain, Miss ELSIE STEPHENSON, director of Edinburgh University's nursing studies unit, said that details were being worked out in co-operation with selected hospitals in the city. (*Glasgow Herald*, May 7.)

"Agressologie"

A new French journal, *Agressologie, Revue Internationale de Physio-biologie et de Pharmacologie appliquées aux Effets de l'Agression*, dealing with the effects of sudden physical stress, is to be published quarterly. Each article will be summarized in English, German, and Spanish, and the editor is Dr. H. LABORIT, Laboratoire d'Eutonologie, Hôpital Boucicaut, Paris, 15. The correspondent in Great Britain is Mr. G. E. HALE ENDERBY. The annual

subscription is 55 N.F., or 20 N.F. for a single copy. Further details may be obtained from the publishers: S.P.E.I., 14, Rue Drouot, Paris, 9.

Change of Title

The journal of the Netherlands Society of Psychiatry and Neurology is now to be called *Psychiatria, Neurologia, Neurochirurgia.* It used to be *Folia Psychiatrica, Neurologica et Neurochirurgica Neerlandica.* It will be published bi-monthly in future by Elsevier Publishing Company, 110–112, Spuistraat, Amsterdam-C, The Netherlands, at a subscription rate of £4 a year.

Compulsory Latin

The positions taken up by the Universities of Oxford and Cambridge over compulsory Latin in future matriculation requirements are now clear. In effect, the Oxford scheme (Scheme C) requires a classical language of those who have not passed at advanced level in mathematics or a science subject, while Cambridge (Scheme B) does not. Scheme B won an easy victory in the Cambridge University Regent House ballot held on May 10. It requires a pass at G.C.E. level in the use of English, two languages, mathematics, or a science subject, and one other subject, provided that two approved subjects have been passed at advanced level.

Care of Handicapped Children

A training scheme for men and women who wish to look after handicapped children in boarding-schools and homes has been announced by Sir DAVID ECCLES, Minister of Education. The Secretary, the Central Training Council in Child Care, Horseferry House, Thorney Street, London, S.W.1, will supply details and application forms.

New Surgical Neurology Department, Edinburgh

The new £500,000 department of surgical neurology at the Western General Hospital, Edinburgh, which has 60 beds and two operating-theatre suites, has been described as one of the most advanced departments of its kind in the world.

There are three ward units of four four-bed and four single wards, and each bed is equipped with two-station radio, a call-light system, power plugs, oxygen and suction outlets, and built-in wardrobe accommodation. There are extensive facilities for radiography, and a dark room with two circulations for processing radiographs and angiographies. Surgeons and nurses and patients and anaesthetists approach the two operating theatres by two separate routes. Each operating theatre has as its ceiling an egg-shaped aluminium pressurized dome which contains operating-lights 10 times as powerful as normal theatre lights, ventilation grilles, and viewing-ports. Each theatre is also equipped with a five-way radiographic viewing-box, a magnetic lighting-control panel, oxygen, nitrous-oxide suction, nitrogen for compression tools, E.E.G. connexions, and television for the transmission of encephalograph recordings. Professor N. DOTT, professor of neurological surgery at Edinburgh University, is to be in charge of the new unit.

Strontium-90 Report

Strontium-90 in Human Bone in the U.K., 1956–1958, is a simplified account by a U.K.A.E.A. research group of the role of strontium and calcium in the body, together with an appraisal of previously published measurements of the deposition of strontium in bone (H.M.S.O., 6s. net). The most recent of the Atomic Energy Authority's six-monthly reports on the subject which gave some figures for the early part of 1959 was discussed in the *Journal,* April 9, p. 1117.

Isotope Research Laboratories

A research centre for the development of radioactive isotopes, housed in laboratories costing £750,000, was opened at Wantage, Berkshire, on May 16 by Lord HAILSHAM, Minister for Science. Experiments will be carried out there in the sterilization and preservation of goods by radiation.

Medical Book Competition

Prizes totalling £1,000 are being offered for full-length prose works with a medical background or interest in two categories: (1) a romantic novel, (2) a work of fiction or non-fiction, other than a medical textbook, that does not come into the first category. The closing date is June 1, 1961, and six weeks later for overseas competitors. Details can be found on advertisement page 38.

American Monograph Prizes

The American Academy of Arts and Sciences is awarding $1,000 " to the author of an especially meritorious unpublished monograph in the physical and biological sciences," including medicine. Details may be obtained from the Committee on Monograph Prizes, American Academy of Arts and Sciences, Little Hall, 33, Harvard University, Cambridge, 38, Massachusetts, U.S.A. The closing date is October 1.

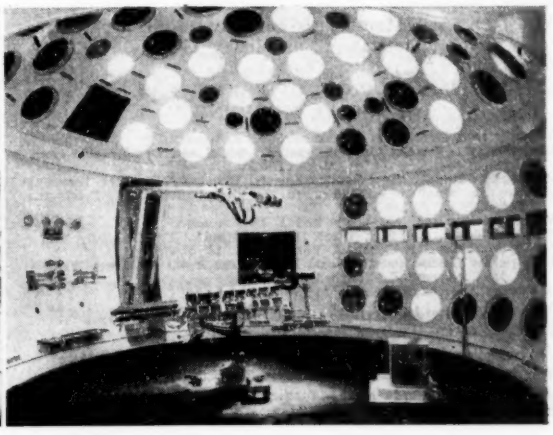
Nuffield Grant to Great Ormond Street

A special Nuffield Foundation grant of £5,000 to the Institute of Child Health, the Hospital for Sick Children, Great Ormond Street, will be used to employ extra chemists who will test for chemical abnormalities all mentally retarded children going to the hospital.

People in the News

Mr. L. T. MORTON, formerly Information Officer to the *Journal* and now librarian of the National Institute of Medical Research, Mill Hill, London, has been given the Marcia C. Noyes Award by the Medical Library Association of America. The presentation was made at the annual conference of the American Medical Library Association at Kansas City on May 19. This award has hitherto only been made to medical librarians in the United States.

Dr. G. DELACEY has received a Papal Knighthood of the Holy Sepulchre of Jerusalem.



COMING EVENTS

"Eye on Research."—Dr. WILDER PENFIELD, O.M., F.R.S., on the human brain. May 24, B.B.C. TV., 9.15 p.m.

Medical Association for Prevention of War.—Symposium: "Present-day Significance of Medical Science in Relation to War Prevention," chairman: Dr. BARNET STROSS, M.P. May 28, 2.30 p.m., 45, Russell Square, London, W.C.1.

United Hospitals Choir.—Handel's "Belshazzar," United Hospitals Choir and London Choral Orchestra, in aid of World Refugee Year, Chelsea Town Hall, May 31, 7.30 p.m. Tickets from Miss E. SORENSEN, South-western Hospital, Landor Road, London, S.W.9, and at door.

Institute of Dermatology.—Exhibition: June 1–30, Dr. K. V. SANDERSON on "The Architecture of Basal-cell Carcinoma."

Whipps Cross Hospital Medical Society.—Dr. C. CARTER: "Mongolism and Other Conditions due to an Abnormal Number of Chromosomes," Board Room, Whipps Cross Hospital, London, E.11, June 3, 8.30 p.m.

British Association of Urological Surgeons: Home and Overseas.—Annual meeting, London, June 23–25. Details from the Secretary, British Association of Urological Surgeons, 47, Lincoln's Inn Fields, London, W.C.2.

NEW ISSUES

THORAX

The Present Position Relating to Cancer of the Lung. Symposium by the Thoracic Society.
Hazard of Antifoam Emboli from a Bubble Oxygenator. A. B. Cassie, A. G. Riddell, and P. O. Yates.
Tumours of the Lung and the Carcinoid Syndrome. E. D. Williams and J. G. Azzopardi.
Subcutaneous Gas Equilibration in Clinical Practice. Paul Forgacs.
Indirect Estimation of Arterial CO_2 Tension in Emphysema. L. Feinmann, D. J. Newell, and G. B. Pendleton.
Energy Sources of Blood Circulation and the Mechanical Action of the Heart. Leon Manteuffel-Szoege.
The Relation Between Left Atrial Hypertension and Lymphatic Distension in lung Biopsies. Donald Heath and Peter Hicken.
Incarcerated and Obstructed Diaphragmatic Hernia. J. Horton and J. D. S. Hammond.
Tracheal Stenosis in Infancy. John Borrie.
Some Features of the Mitral Valve. E. W. T. Morris.
Unilateral Lung Transradiancy: A Physiological Study. Christopher S. Darke, Alan R. Chrispin, and Beryl S. Snowden.
Pulmonary Manifestations of Staphylococcal Pyaemia. D. R. Hay.
Closed Traumatic Rupture of the Cervical Trachea. E. F. Soothill.
Dr. J. G. Scadding.

Volume 15, No. 1. (Quarterly; £3 annually.)

BRITISH JOURNAL OF OPHTHALMOLOGY

The Central Artery of the Retina. I. Origin and Course. S. Singh and R. Dass.
Experimental Degeneration of the Retina. V. Fasting and Metabolic Accelerators in Degeneration Produced by Sodium Fluoride. A. Sorsby and R. Harding.
Rate of Entrance of Sodium into the Aqueous Humour of the Rabbit. D. F. Cole.
Case of Triple Branching of Retinal Blood Vessel. J. Primrose.
Penicillin Therapy in Trachoma. M. J. Gilkes.
Palpebral Neurilemmoma. S. Mishra and J. Sharan.

Vol. 44, No. 4. (Monthly; £6 annually. With "Ophthalmic Literature" and Index, £9.)

BRITISH JOURNAL OF PREVENTIVE AND SOCIAL MEDICINE

Mortality in a Rural Zulu Community. F. J. Bennett.
Morbidity in a London General Practice. Social and Demographic Data. L. Stein.
Psychiatric Morbidity in a London General Practice. W. I. N. Kessel.
Comparative Study of Attitudes to the Rehabilitation of Psychiatric Patients. S. Folkard.
Young Smokers. A. Cartwright and J. G. Thomson.
British Stillbirths and First Week Deaths, 1950-57. T. M. Allan.
Family Morbidity. J. Cohen, J. Yofe, and A. M. Davies.
Incidence of Gastric and Duodenal Ulcer in the Royal Air Force in 1955. J. H. Baron and R. Vaughan Jones.
A Further Note on Mongolism in Twins. A. Smith.

Volume 14, No. 1. (Quarterly; £3 annually.)

Abstracts of World Medicine.—Issued in the first week of each month, this journal contains abstracts of important papers selected from the current medical literature of the world. Annual subscription £4 4s.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, May 23

INSTITUTE OF DERMATOLOGY.—At British Institute of Radiology, 5 p.m., Dr. P. E. Bodkin: Radiotherapy and Benign Skin Conditions.
MANCHESTER MEDICAL SOCIETY: SECTION OF GENERAL PRACTICE.—At Large Anatomy Theatre, Manchester University Medical School, 8.30 for 9 p.m., Presidential address by Dr. H. W. Ashworth: Hobson's Choice.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor E. P. Sharpey-Schafer: Syncope.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School.—5 p.m., Fourth Almroth Wright Lecture by Dr. P. L. Mollison: Role of Complement in Blood-group Reactions.

Tuesday, May 24

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Professor G. Causey: Some Observations on the Optical and Electron Microscopical Structure of the Skin.
ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute, 5 p.m., Dr. Leonard Easton: Historical Aspects and Modern Views of Management of Retained Placenta.

Wednesday, May 25

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. W. Riddell: Recent Advances in the Study of Ringworm.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Sir Russell Brock: Aortic Stenosis.
LONDON AMATEUR BOXING ASSOCIATION: MEDICAL ADVISORY PANEL.—At British Railways Film Unit, 25, Savile Row, London, W., 8 p.m., Film of European Boxing Championships, Lucerne, 1959.
MANCHESTER MEDICAL SOCIETY: SECTION OF PATHOLOGY.—At Large Anatomy Theatre, Manchester University Medical School, 4.30 for 5 p.m., Professor J. Gough: Recent Advances in the Pathology of Lung Diseases.
OXFORD UNIVERSITY.—At Radcliffe Infirmary, 5 p.m., Litchfield Lecture by Professor Raoul Palmer: Reconstructive Surgery of Fallopian Tubes.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. A. F. B. Standfast: Infection of Mice with *Bordetella* (*Haemophilus*) *pertussis*.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—5 p.m., Morison Lecture by Mr. F. J. Gillingham: Stereotactic Surgery of the Brain: Therapy and Research.
SOCIETY OF CHEMICAL INDUSTRY: NUTRITION PANEL.—At 14, Belgrave Square, S.W., 4 p.m., Dr. L. J. Teply (Chief, Expanded Aid to Nutrition, U.N.I.C.E.F., New York): Foods for the Underdeveloped Countries.

Thursday, May 26

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. P. D. Samman: The Cutaneous Reticuloses.
LONDON UNIVERSITY.—At King's College, Strand, W.C., 5.30 p.m., special university lecture in pharmacology by Professor P. Waser (Zürich): The Cholinergic Receptor.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor M. L. Rosenheim: Phaeochromocytoma.
ST. ANDREWS UNIVERSITY.—At Lecture Theatre, Physiology Department, Queen's College, Small's Wynd, Dundee, 5 p.m., Dr. Frangcon Roberts: Acceptance of the Scientific Method of Medicine—Its Origin, Evolution, and Consequences.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., postgraduate demonstration by Dr. Hamilton Paterson: Neurology.
UNIVERSITY COLLEGE LONDON: DEPARTMENT OF BIOCHEMISTRY.—At Physiology Theatre, Gower Street, W.C., 5 p.m., public lecture by Dr. S. J. Bach: Metabolic Fate of Protein-Nitrogen in the Mammal—(I) Utilization of Amino-Nitrogen of Protein Constituents.

Friday, May 27

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. D. Porter: clinical dermatology.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Sir Russell Brock: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Mr. George Qvist: Surgery of the Lower Oesophagus.
INSTITUTE OF NEUROLOGY.—4.30 p.m., Mr. Valentine Logue: Surgical Management of Cerebral Aneurysms.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., Mr. Ashton Miller: Paediatric Urology.
ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At Manson Theatre, London School of Hygiene and Tropical Medicine, 5.30 p.m., annual general meeting, followed by symposium on related variables in medical statistics. Dr. N. T. J. Bailey, Multiple Regression in Hospital Costing: Mr. T. H. Hollingsworth, Discriminant Functions in the Diagnosis of Lung Cancer; Dr. A. E. Maxwell, Factor Analysis in Clinical Psychology.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Cassells.—On May 4, 1960, at Thames Ditton, Surrey, William Leonard Cassells, M.B., Ch.B., formerly of 60, London Road, Twickenham.
Cheyney.—On May 7, 1960, George Hammond Cheyney, M.R.C.S., L.R.C.P., of 5, Priory Avenue, Caversham, Reading Berks.
Eagland.—On May 5, 1960, in London, Raymond David Eagland, M.B., B.Chir., of Cambridge and Malaya.
Hadden.—On May 4, 1960, at Magharee House, Portadown, Co. Armagh, Winifred Eileen Hadden, M.D., D.P.H.
Langdale.—On May 3, 1960, Harry Marmaduke Langdale, M.R.C.S., L.R.C.P., Surgeon-Captain, R.N., retired.
Ryan.—On April 24, 1960, at Wardour, Wilts, James Michael Joseph Ryan, M.B., B.Ch., Colonel, late R.A.M.C. retired.
Scott.—On April 23 1960, William Graham Scott, L.R.C.P.&S.Ed., L.R.F.P.S., of 1, Sedbergh Road, Kendal, Westmorland, formerly of Broomhill, Northumberland, aged 82.
Silvester.—On April 28, 1960, at the Brook Hospital, London, S.E., Temple St. John Hudson Silvester, M.R.C.S., L.R.C.P.
Waugh.—On April 25, 1960, at Drayton Valley, Alberta, Canada, William Grant Waugh, M.D., F.R.C.S.Ed., late of Sunderland, Co. Durham, and Harley Street, London, W., aged 73.
Yates.—On April 23, 1960, at the Royal Hospital, Putney, London, S.W., Irene Yates, M.D., M.R.C.P., D.P.M., late of Enniscorthy, Co. Wexford.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Pernicious Anaemia and Pregnancy

Q.—*Pernicious anaemia was diagnosed one year ago in a woman of 34. She has been married 6 years and had been sterile. Now she is four months pregnant. Is pregnancy unusual in a case of treated pernicious anaemia, and could it cause sterility? Are any special precautions needed during the antenatal period?*

A.—Pernicious anaemia (as distinct from the macrocytic anaemia of pregnancy) is not very commonly seen in pregnant women, for the reason that it is a disease which does not usually manifest itself until after the childbearing age. Possibly for the same reason pernicious anaemia is not an accepted cause for sterility, but it cannot be denied that in a young woman it might, by interfering with general health, ovulation, and implantation of the fertilized ovum, lower fertility.

The patient in question deserves special care both during the antenatal and intranatal periods, partly because of the anaemia and partly because she is an elderly primigravida with a history of infertility. Assuming that the anaemia is already being treated with vitamin B_{12}, the dose needs to be increased during pregnancy because of foetal demands. Treatment should, however, be governed by frequent checks on the blood picture. Apart from this, arrangements should be made for her to be delivered in a fully equipped maternity unit, and special watch kept for the early signs of toxaemia and for the other well-known hazards of pregnancy and labour to which this class of patient is particularly subject.

Corticosteroids and Foetal Abnormality

Q.—*Is there any risk of a malformed foetus when either of the parents is being treated with a corticosteroid at the time of conception?*

A.—There is no evidence that when pregnancy occurs in a woman receiving cortisone, whether substitutional or additional, the chances of foetal malformation are increased.[1 2] Corticosteroid therapy may decrease the sperm count in a male, but again there is no evidence that the incidence of foetal abnormalities is increased thereby.

REFERENCES

1 Merrill, J. A., *Obstet. and Gynec.*, 1955, **6**, 637.
2 Bret, J., *Rev. franç. Gynéc.*, 1958, **53**, 855.

Infectiousness of Rheumatic Fever

Q.—*Is acute rheumatic fever of the juvenile type regarded as an infectious disease?*

A.—Rheumatic fever is an acute or chronic inflammatory process initiated by a preceding group-A haemolytic streptococcal infection. In streptococcal epidemics up to 3% of cases may develop rheumatic sequelae,[1] but the normal incidence is probably lower.[2] In a given population, therefore, the more group-A haemolytic streptococcal infections of the upper respiratory tract the more rheumatic fever, and the declining incidence of the latter in this country in the last few decades is undoubtedly associated with decreased spread of streptococci due to less overcrowding. The prevalence of acute rheumatic fever is thus influenced by factors which affect the spread of respiratory infection.

Rheumatic fever itself, however, is not an infectious disease, and its low incidence following streptococcal infections indicates that other important factors, mostly unknown, determine its appearance. While there is little evidence for the existence of "rheumatogenic" types of group-A streptococci, there are grounds for believing that genetic host factors play a part in determining susceptibility.[3] One attack of rheumatic fever makes a second and subsequent attack very much more likely, and the importance of control of infection in the management of rheumatic fever arises from the established fact that antibiotic prophylaxis and treatment of streptococcal infection in rheumatic subjects very greatly reduces this likelihood.[4]

REFERENCES

1 *Rheumatic Fever* (ed. Lewis Thomas), Minneapolis, 1952.
2 Holmes, M. C., and Williams, R. E. O., *J. Hyg.*, 1958, **56**, 43.
3 Glynn, A. A., Glynn, L. E., and Holborow, E. J., *Brit. med. J.*, 1959, **2**, 266.
4 Further Report of the Rheumatic Fever Committee of the Royal College of Physicians, 1957. London.

Chemotherapy Before Diagnosis

Q.—*What chemotherapy should be given in undiagnosed febrile illnesses in children in general practice?*

A.—The ideal policy is to use chemotherapy only after a diagnosis has been made. This, however, is not always possible in practice. When used without an established diagnosis, it should be restricted to illnesses in which it is felt either that delay would be dangerous or while awaiting the result of some investigation such as urinanalysis.

Using the above criteria, if a urinary infection is suspected in an infant, there is no urgency, and it would be wise to withhold chemotherapy until microscopy of urine has been carried out and, if possible, culture. I would not advise the empirical use of tetracycline, since it readily penetrates the theca and thus can mask a meningitis very effectively. There are also the dangers of its producing side-effects, such as diarrhoea or monilial infections of the mouth. It may also produce resistant organisms, the most important being *Staphylococcus aureus*.

It seems, therefore, that empirical chemotherapy should be restricted to penicillin or sulphonamides, if meningitis can be excluded. The broad-spectrum group should be restricted to diagnosed illness in general practice, and if used it should always be in full dosage and for a period of not more than six days.

Safety of Drinking-water

Q.—*What precautions should be taken on a holiday when the safety of tap-water for drinking is in doubt?*

A.—Whenever in doubt about a water supply it is always advisable to drink one of the many brands of bottled water that are available in hotels generally on the Continent. Failing this, treatment of small quantities of water is possible provided it is clear of any suspended matter. Straining the water through fine cotton or linen material, such as a clean handkerchief, will remove any suspended material. Clear water can be sterilized by raising and maintaining its temperature to boiling point for about five minutes, or by the addition of one of the following chemical sterilizing agents.

(1) Weak sodium hypochlorite solution, such as "milton" (1% available chlorine). The dose is 4 drops to 1 quart (1.1 litres) of water; leave for 30 minutes before use. If the treated water tastes of chlorine, add one or two crystals of sodium thiosulphate (photographic "hypo") and stir to dissolve and mix.

(2) Tablets containing available chlorine are also available, namely, "halazone" (Boots Ltd.). One tablet suffices for 1 quart of water, which can be drunk after a contact time of 30 minutes.

(3) Iodine is also effective for the disinfection of water in doses of 1 drop of tincture of iodine to 1 quart of water, again with a contact time of 30 minutes.

More information on the treatment of small quantities of water can be found in Bulletin No. 10 of the Ross Institute Industrial Advisory Committee, published in 1955. A further precaution recommended is protection obtained by a recent T.A.B. inoculation.

Pustular Acne

Q.—*What is the best treatment for long-standing, severe pustular acne in a man? It appears to be aggravated by fatty foods.*

A.—Many patients with acne seem to find that their eruption is made worse by eating chocolate or other fatty foods. Chocolate and all pork fats are best avoided, and probably also milk fats, including cheese, should be eliminated from the diet. Margarine and vegetable cooking fats are allowed.

The application of sulphur to the skin is usually beneficial. Resorcin and sulphur paste, *B.N.F.*, may be applied at night, and should be washed off again in the morning. If it proves too strong it may be diluted with equal parts of ung. emulsificans. Ultra-violet light is valuable in some cases but not in all. The dose should be one which produces a mild erythema twice weekly for a period of four to six weeks. Exposure to natural sunlight is often helpful.

A short course of an antibiotic is often extremely valuable when pustules are numerous. Chloramphenicol or tetracycline are suitable for this purpose. Sulphonamides are also sometimes used, but their value is not so certain. Most severe cases need *x*-ray treatment, a total of 400 to 600 r being given in divided doses over a period of three or four weeks. In this dosage *x*-ray treatment is usually of considerable benefit and has no harmful sequelae.

The management of a severe case requires a good deal of attention on the part of the physician, the treatment being varied according to the progress made and the various methods outlined above used simultaneously or in turn. In a severe case one can seldom hope to clear up the eruption completely, but it is nearly always possible with perseverance to produce a substantial improvement.

Relieving Cardiospasm

Q.—*What are the best medical means for relieving the symptoms of cardiospasm? Would the passage of a tube after meals relieve the distension of the oesophagus? Has any drug proved useful?*

A.—Cardiospasm is due to failure of relaxation of the lower end of the oesophagus. In some cases sniffing octyl nitrite may facilitate swallowing, but usually some form of dilatation is necessary. There is no point in passing a tube after meals, although a mercury bougie may be passed beforehand, but to-day this is seldom done. In practice, any troublesome case is far better after having either a brusque dilatation or a Heller's operation.

Postponement of Immunizations

Q.—*What is the rationale of postponing immunizations in a patient who has either an active infection or may be incubating an infection after a known exposure? Does the type of infection—i.e., viral or bacterial—make any difference to the rule? For how long after recovery should immunizations be postponed?*

A.—The main reason for postponing immunizations in these circumstances is that the symptoms resulting from either event—the infection or the immunization—may be exacerbated. This applies to active immunization rather than passive: obviously tetanus antitoxin must be given as soon as possible in tetanus-prone cases, even if the subject may be incubating tetanus. The administration of many vaccines, such as T.A.B., may entail considerable constitutional disturbance, which could aggravate certain co-existing infections. In general, there would be little difference between an overt infection and one which might be late in the incubation period: nor would it matter whether the infection were bacterial or viral.

In addition to true infections, the allergic condition of infantile eczema would preclude vaccination against smallpox. A history of convulsions would be a contraindication to pertussis vaccination.

One vaccine, T.A.B., has given rise to much discussion from the standpoint of its use in periods of epidemic prevalence of enteric fever. Some authorities believe that in an epidemic vaccination with T.A.B. should be stopped, whereas others think that it should be intensified. There is as yet no agreement on this point.

The period of postponement of various vaccinations need be quite short—generally only as long as it takes for full recovery from the effects of the infection.

Priapism and Chlorothiazide

Q.—*Is painful priapism at night a known complication in male patients receiving chlorothiazide together with a potassium chloride mixture for cardiac insufficiency?*

A.—Priapism is not a recognized complication of chlorothiazide treatment. Nor is a potassium mixture likely to have this effect. It seems more probable that the priapism is the result of some local disorder, such as prostatism, or of some generalized disease, and these possibilities should be looked into. Presumably pelvic congestion precipitates the priapism, and it would be interesting to know if a profuse diuresis occurs at night. If so, priapism might be avoided if the diuretic is given only in the morning.

Inheritance of Epilepsy

Q.—*A's grandfather married twice. There were four girls from the second marriage, one of whom has severe epilepsy. A is about to marry one of the other three. What are the chances of their having an epileptic child? None of the 10 children (of whom A's father is one) of the grandfather's first marriage are epileptics.*

A.—There is no great risk of this couple having epileptic children. Genetically, they are equivalent to first cousins, but there is no evidence at the moment that grand mal might be due to recessive genes.

NOTES AND COMMENTS

Ocular Effects of Ultra-violet Light.—Dr. J. P. CARLILE (Norwich) writes: With reference to your answer on the ocular effects of ultra-violet light ("Any Questions?" April 30, p. 1378), "Chance's Crookes A glass" should be asked for if one is to be certain of getting the desired optical formula. *Which*, the journal of the Consumers Association, dealt with this matter in its autumn issue, 1957. It would appear that the patent has expired, so that glasses marked "Crookes lens" or "Crookes glass" need not, and in fact often does not, mean the lens is made from the formula originally patented by Messrs. Chance.

Correction.—In the letter from Mr. Frank Robinson (May 7, p. 1430) the first sentence of the third paragraph should have ended as follows, "but more (not none) of these cases should be treated by early excision and grafting."

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